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(54) **3',5'-CYCLIC PHOSPHATE PRODRUGS FOR HCV INFECTION**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Provided herein are compounds, compositions and methods for the treatment of Flaviviridae infections, including HCV infections. In certain embodiments, compounds and compositions of nucleoside derivatives are disclosed, which can be administered either alone or in combination with other antiviral agents.

21 Claims, No Drawings

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3',5'-CYCLIC PHOSPHATE PRODRUGS FOR HCV INFECTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of, and priority to, U.S. provisional patent application No. 61/650,415 entitled "3',5'-CYCLIC PHOSPHATE PRODRUGS FOR HCV INFECTION" which was filed May 22, 2012 and is hereby incorporated by reference. This application also claims the benefit of, and priority to, U.S. provisional patent application No. 61/695,221 entitled "3',5'-CYCLIC PHOSPHATE PRODRUGS FOR HCV INFECTION" which was filed Aug. 30, 2012 and is hereby incorporated by reference.

FIELD

Provided herein are compounds, methods and pharmaceutical compositions for use in treatment of viral infections, including hepatitis C virus infections in hosts in need thereof. In certain embodiments, 3',5'-cyclic phosphate prodrug nucleotides are provided which display remarkable efficacy and bioavailability for the treatment of, for example, HCV infection in a human.

BACKGROUND

The hepatitis C virus (HCV) is the leading cause of chronic liver disease worldwide. (Boyer, N. et al., *J. Hepatol.* 32:98-112, 2000). HCV causes a slow growing viral infection and is the major cause of cirrhosis and hepatocellular carcinoma (Di Besceglie, A. M. and Bacon, B. R., *Scientific American*, October: 80-85, 1999; Boyer, N. et al., *J. Hepatol.* 32:98-112, 2000). It is estimated there are about 130-170 million people with chronic hepatitis C virus infection, and there are about 350,000 deaths from hepatitis C-related liver diseases each year (Hepatitis C Fact Sheet, *World Health Organization Fact Sheet No.* 164, June 2011). Cirrhosis caused by chronic hepatitis C infection accounts for 8,000-12,000 deaths per year in the United States, and HCV infection is the leading indication for liver transplantation.

HCV infection becomes chronic in about 75% of cases, with many patients initially being asymptomatic. The first symptoms of HCV infection are often those of chronic liver disease. About 20 to 30% of patients with chronic hepatitis due to HCV develop cirrhosis, although this may take decades. Development of cirrhosis due to HCV also increases the risk of hepatocellular cancer (The Merck Manual Online, Chronic Hepatitis, available at www.merckmanuals.com/professional/hepatic_and_biliary disorders/hepatitis/chronic_hepatitis.html, last revision February 2007).

In light of the fact that HCV infection has reached epidemic levels worldwide, and has tragic effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat hepatitis C that have low toxicity to the host. Further, given the rising threat of other flaviviridae infections, there remains a strong need to provide new effective pharmaceutical agents that have low toxicity to the host. Therefore, there is a continuing need for effective treatments of flavivirus infections and HCV infections.

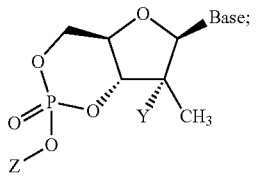
SUMMARY

Provided herein are compounds useful, for example, for the treatment of flavivirus infections such as HCV infections. The compounds are 3',5'-cyclic phosphate prodrugs. In certain embodiments the 3',5'-cyclic phosphate prodrugs display remarkable efficacy or bioavailability, or both, for the treatment of, for example, HCV infection in a human.

In certain embodiments, the compounds provided herein are useful in the prevention and treatment of Flaviviridae infections and other related conditions such as anti-Flaviviridae antibody positive and Flaviviridae-positive conditions, chronic liver inflammation caused by HCV, cirrhosis, fibrosis, acute hepatitis, fulminant hepatitis, chronic persistent hepatitis, and fatigue. These compounds or formulations can also be used prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-Flaviviridae antibody or Flaviviridae-antigen positive or who have been exposed to a Flaviviridae. In particular embodiments, the Flaviviridae is hepatitis C. In certain embodiments, the compounds are used to treat any virus that replicates through an RNA-dependent RNA polymerase.

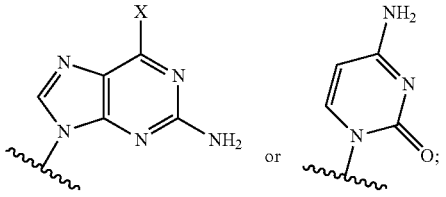
A method for the treatment of a Flaviviridae infection in a host, including a human, is also provided that includes administering an effective amount of a compound provided herein, administered either alone or in combination or alternation with another anti-Flaviviridae agent, optionally in a pharmaceutically acceptable carrier.

In certain embodiments, provided herein are compounds of Formula (VIII):

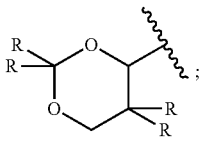


(VIII)

or a pharmaceutically acceptable salt, solvate, stereoisomeric form, tautomeric form or polymorphic form thereof, wherein: each Base is independently



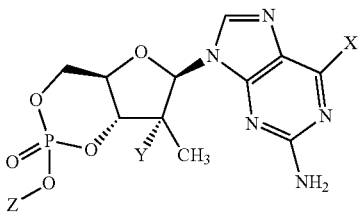
each X is independently alkoxyl, hydrogen, or hydroxyl; each Y is independently hydroxyl, acetoxyl, or fluoro; each Z is independently $-LC(O)O(L)_pCR_3$, -L-Ar—$C(O)O(L)_pCR_3$, —$CR(E)(L)_pOC(O)O(L)_pCR_3$, -LSC(O)LOH, -LSC(O)$LOC(O)(L)_pCR_3$, -LSC(O)$LOC(O)(L)_pNR_2$, -LS-$S(L)_pCR_3$, -LS-SLOH, -LNRC(O)$O(L)_pCR_3$, -LSC(O)LNRC(O)$O(L)_p$ CR_3, —Ar—B, -L-B, -LNRC(O)D, -LNRC(O)CH$(OH)(CR_2)_2OH$, or $-(L)_pCR(R^4)C(O)O(L)_pCR_3$; each B is independently an alkyl group substituted with aminocarboxylene, carboxylene, or both; each D is independently



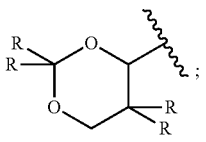
each E is independently alkyl, substituted alkyl, aryl, or heteroaryl; each Ar is independently an arylene or heteroarylene; each L is independently alkylene or substituted alkylene; each R is independently hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl; each R^A is independently a carbocyclic or heterocyclic ring; and each p is independently 0 or 1.

In certain embodiments, provided herein are compounds according to Formula I:

(I)



or pharmaceutically acceptable salts, solvates, stereoisomeric forms, tautomeric forms or polymorphic forms thereof, wherein: each X is independently alkoxyl, hydrogen, or hydroxyl; each Y is independently hydroxyl, acetoxyl, or fluoro; each Z is independently -LC(O)O(L)$_p$CR$_3$, -L-Ar—C(O)O(L)$_p$CR$_3$, —CR(E)(L)$_p$OC(O)O(L)$_p$CR$_3$, -LSC(O)LOH, -LSC(O)LOC(O)(L)$_p$CR$_3$, -LSC(O)LOC(O)(L)$_p$NR$_2$, -LS-S(L)$_p$CR$_3$, -LS-SLOH, -LNRC(O)O(L)$_p$CR$_3$, -LSC(O)LNRC(O)O(L)$_p$CR$_3$, —Ar—B, -L-B, -LNRC(O)D, -LNRC(O)CH(OH)(CR$_2$)$_2$OH, or -(L)$_p$CR(R^A)C(O)O(L)$_p$CR$_3$; each B is independently an alkyl group substituted with aminocarboxylene, carboxylene, or both; each D is independently



each E is independently alkyl, substituted alkyl, aryl, or heteroaryl; each Ar is independently an arylene or heteroarylene; each L is independently alkylene or substituted alkylene; each R is independently hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl; each R^A is independently a carbocyclic or heterocyclic ring; and each p is independently 0 or 1.

In one aspect, the compounds provided herein are provided or administered in combination with a second therapeutic agent, such as one useful for the treatment or prevention of HCV infections. Exemplary second therapeutic agents are provided in detail elsewhere herein.

In another aspect, provided herein are pharmaceutical compositions, single unit dosage forms, and kits suitable for use in treating or preventing disorders such as HCV infections which comprise a therapeutically or prophylactically effective amount of a compound provided herein, e.g., of Formula I, and a therapeutically or prophylactically effective amount of a second therapeutic agent such as one useful for the treatment or prevention of HCV infections.

In certain embodiments, a method of treatment of a liver disorder is provided comprising administering to an individual in need thereof a treatment effective amount of a 3',5'-cyclic phosphate prodrug compound.

Flaviviridae which can be treated are, e.g., discussed generally in Fields Virology, Fifth Ed., Editors: Knipe, D. M., and Howley, P. M., Lippincott Williams & Wilkins Publishers, Philadelphia, Pa., Chapters 33-35, 2006. In a particular embodiment of the invention, the Flaviviridae is HCV. In an alternate embodiment, the Flaviviridae is a flavivirus or pestivirus. In certain embodiments, the Flaviviridae can be from any class of Flaviviridae. In certain embodiments, the Flaviviridae is a mammalian tick-borne virus. In certain embodiments, the Flaviviridae is a seabird tick-borne virus. In certain embodiments, the Flaviviridae is a mosquito-borne virus. In certain embodiments, the Flaviviridae is an Aroa virus. In certain embodiments, the Flaviviridae is a Dengue virus. In certain embodiments, the Flaviviridae is a Japanese encephalitis virus. In certain embodiments, the Flaviviridae is a Kokobera virus. In certain embodiments, the Flaviviridae is a Ntaya virus. In certain embodiments, the Flaviviridae is a Spondweni virus. In certain embodiments, the Flaviviridae is a Yellow fever virus. In certain embodiments, the Flaviviridae is a Entebbe virus. In certain embodiments, the Flaviviridae is a Modoc virus. In certain embodiments, the Flaviviridae is a Rio Bravo virus.

Specific flaviviruses include, without limitation: Absettarov, Aedes, Alfuy, Alkhurma, Apoi, Aroa, Bagaza, Banzi, Bukalasa bat, Bouboui, Bussuquara, Cacipacore, Calbertado, Carey Island, Cell fusing agent, Cowbone Ridge, Culex, Dakar bat, Dengue 1, Dengue 2, Dengue 3, Dengue 4, Edge Hill, Entebbe bat, Gadgets Gully, Hanzalova, Hypr, Ilheus, Israel turkey meningoencephalitis, Japanese encephalitis, Jugra, Jutiapa, Kadam, Kamiti River, Karshi, Kedougou, Kokobera, Koutango, Kumlinge, Kunjin, Kyasanur Forest disease, Langat, Louping ill, Meaban, Modoc, Montana myotis leukoencephalitis, Murray valley encephalitis, Nakiwogo, Naranjal, Negishi, Ntaya, Omsk hemorrhagic fever, Phnom-Penh bat, Powassan, Quang Binh, Rio Bravo, Rocio, Royal Farm, Russian spring-summer encephalitis, Saboya, St. Louis encephalitis, Sal Vieja, San Perlita, Saumarez Reef, Sepik, Sokuluk, Spondweni, Stratford, Tembusu, Tick-borne encephalitis, Turkish sheep encephalitis, Tyuleniy, Uganda S, Usutu, Wesselsbron, West Nile, Yaounde, Yellow fever, Yokose, and Zika.

Pestiviruses which can be treated are discussed generally in Fields Virology, Fifth Ed., Editors: Knipe, D. M., and Howley, P. M., Lippincott Williams & Wilkins Publishers, Philadelphia, Pa., Chapters 33-35, 2006. Specific pestiviruses include, without limitation: bovine viral diarrhea virus ("BVDV"), classical swine fever virus ("CSFV," also called hog cholera virus), and border disease virus ("BDV").

DESCRIPTION OF EXEMPLARY EMBODIMENTS

Provided herein are compounds, compositions and methods useful for treating liver disorders such as HCV infection in a subject. Further provided are dosage forms useful for such methods.

DEFINITIONS

When referring to the compounds provided herein, the following terms have the following meanings unless indi-

cated otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

The term "alkyl", as used herein, unless otherwise specified, refers to a saturated straight or branched hydrocarbon. In certain embodiments, the alkyl group is a primary, secondary, or tertiary hydrocarbon. In certain embodiments, the alkyl group includes one to ten carbon atoms, i.e., C_1 to C_{10} alkyl. In certain embodiments, the alkyl group is selected from the group consisting of methyl, CF_3, CCl_3, $CFCl_2$, CF_2Cl, ethyl, CH_2CF_3, CF_2CF_3, propyl, isopropyl, butyl, isobutyl, secbutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The term includes both substituted and unsubstituted alkyl groups, including halogenated alkyl groups. In certain embodiments, the alkyl group is a fluorinated alkyl group. Non-limiting examples of moieties with which the alkyl group can be substituted are selected from the group consisting of halogen (fluoro, chloro, bromo or iodo), hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, hereby incorporated by reference.

The term "lower alkyl", as used herein, and unless otherwise specified, refers to a saturated straight or branched hydrocarbon having one to six carbon atoms, i.e., C_1 to C_6 alkyl. In certain embodiments, the lower alkyl group is a primary, secondary, or tertiary hydrocarbon. The term includes both substituted and unsubstituted moieties.

The term "cycloalkyl", as used herein, unless otherwise specified, refers to a saturated cyclic hydrocarbon. In certain embodiments, the cycloalkyl group may be a saturated, and/or bridged, and/or non-bridged, and/or a fused bicyclic group. In certain embodiments, the cycloalkyl group includes three to ten carbon atoms, i.e., C_3 to C_{10} cycloalkyl. In some embodiments, the cycloalkyl has from 3 to 15 (C_{3-15}), from 3 to 10 (C_{3-10}), or from 3 to 7 (C_{3-7}) carbon atoms. In certain embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, cycloheptyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, decalinyl, or adamantyl.

The term "cycloalkenyl", as used herein, unless otherwise specified, refers to an unsaturated cyclic hydrocarbon. In certain embodiments, cycloalkenyl refers to mono- or multicyclic ring systems that include at least one double bond. In certain embodiments, the cycloalkenyl group may be a bridged, non-bridged, and/or a fused bicyclic group. In certain embodiments, the cycloalkyl group includes three to ten carbon atoms, i.e., C_3 to C_{10} cycloalkyl. In some embodiments, the cycloalkenyl has from 3 to 7 (C_{3-10}), or from 4 to 7 (C_{3-7}) carbon atoms.

"Alkylene" refers to divalent saturated aliphatic hydrocarbon groups particularly having from one to eleven carbon atoms which can be straight-chained or branched. In certain embodiments, the alkylene group contains 1 to 10 carbon atoms. The term includes both substituted and unsubstituted moieties. This term is exemplified by groups such as methylene (—CH_2—), ethylene (—CH_2CH_2—), the propylene isomers (e.g., —$CH_2CH_2CH_2$— and —$CH(CH_3)CH_2$—) and the like.

"Alkenyl" refers to monovalent olefinically unsaturated hydrocarbon groups, in certain embodiment, having up to about 11 carbon atoms, from 2 to 8 carbon atoms, or from 2 to 6 carbon atoms, which can be straight-chained or branched and having at least 1 or from 1 to 2 sites of olefinic unsaturation. The term includes both substituted and unsubstituted moieties. Exemplary alkenyl groups include ethenyl (i.e., vinyl, or —CH=CH_2), n-propenyl (—CH_2CH=CH_2), isopropenyl (—$C(CH_3)$=CH_2), and the like.

"Alkenylene" refers to divalent olefinically unsaturated hydrocarbon groups, in certain embodiments, having up to about 11 carbon atoms or from 2 to 6 carbon atoms which can be straight-chained or branched and having at least 1 or from 1 to 2 sites of olefinic unsaturation. This term is exemplified by groups such as ethenylene (—CH=CH—), the propenylene isomers (e.g., —CH=$CHCH_2$— and —$C(CH_3)$=CH— and —CH=$C(CH_3)$—) and the like.

"Alkynyl" refers to acetylenically unsaturated hydrocarbon groups, in certain embodiments, having up to about 11 carbon atoms or from 2 to 6 carbon atoms which can be straight-chained or branched and having at least 1 or from 1 to 2 sites of alkynyl unsaturation. Non-limiting examples of alkynyl groups include acetylenic, ethynyl (—C≡CH), propargyl (—CH_2C≡CH), and the like.

The term "aryl", as used herein, and unless otherwise specified, refers to phenyl, biphenyl, or naphthyl. The term includes both substituted and unsubstituted moieties. An aryl group can be substituted with any described moiety, including, but not limited to, one or more moieties selected from the group consisting of halogen (fluoro, chloro, bromo or iodo), alkyl, haloalkyl, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., *Protective Groups in Organic Synthesis*, John Wiley and Sons, Second Edition, 1991.

"Alkoxy" or "alkoxyl" as used herein refers to the group —OR' where R' is alkyl or cycloalkyl. Alkoxy groups include, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like.

"Acetoxy" or "Acetoxyl" as used herein refers to the group —$OC(O)CH_3$.

"Alkoxycarbonyl" refers to a radical —C(O)-alkoxy where alkoxy is as defined herein.

"Amino" refers to the radical —NH_2.

"Carboxyl" or "carboxy" refers to the radical —C(O)OH. "Carboxylene" refers to the radical —C(O)O—.

The term "aminocarboxylene" refers to the radical —C(O)ONH_2 or —$OC(O)NH_2$. In certain embodiments, the term "aminocarboxylene" refers to the radical —$C(O)ONH_2$. In certain embodiments, the term "aminocarboxylene" refers to the radical —$OC(O)NH_2$.

The term "alkylamino" or "arylamino" refers to an amino group that has one or two alkyl or aryl substituents, respectively. In certain embodiments, the alkyl substituent is lower alkyl. In another embodiment, the alkyl or lower alkyl is unsubstituted.

"Halogen" or "halo" refers to chloro, bromo, fluoro or iodo.

"Monoalkylamino" refers to the group alkyl-NR'—, wherein R' is selected from hydrogen and alkyl or cycloalkyl.

"Thioalkoxy" refers to the group —SR' where R' is alkyl or cycloalkyl.

The term "heterocyclyl" or "heterocyclic" refers to a monovalent monocyclic non-aromatic ring system and/or multicyclic ring system that contains at least one non-aromatic ring, wherein one or more of the non-aromatic ring

atoms are heteroatoms independently selected from O, S, or N; and the remaining ring atoms are carbon atoms. In certain embodiments, the heterocyclyl or heterocyclic group has from 3 to 20, from 3 to 15, from 3 to 10, from 3 to 8, from 4 to 7, or from 5 to 6 ring atoms. Heterocyclyl groups are bonded to the rest of the molecule through the non-aromatic ring. In certain embodiments, the heterocyclyl is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include a fused or bridged ring system, and in which the nitrogen or sulfur atoms may be optionally oxidized, the nitrogen atoms may be optionally quaternized, and some rings may be partially or fully saturated, or aromatic. The heterocyclyl may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heterocyclic radicals include, but are not limited to, azepinyl, benzodioxanyl, benzodioxolyl, benzofuranonyl, benzopyranonyl, benzopyranyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, benzothiopyranyl, benzoxazinyl, β-carbolinyl, chromanyl, chromonyl, cinnolinyl, coumarinyl, decahydroisoquinolinyl, dihydrobenzisothiazinyl, dihydrobenzisoxazinyl, dihydrofuryl, dihydroisoindolyl, dihydropyranyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4-dithianyl, furanonyl, imidazolidinyl, imidazolinyl, indolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isochromanyl, isocoumarinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, oxazolidinonyl, oxazolidinyl, oxiranyl, piperazinyl, piperidinyl, 4-piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydrothienyl, thiamorpholinyl, thiazolidinyl, tetrahydroquinolinyl, and 1,3,5-trithianyl. In certain embodiments, heterocyclic may also be optionally substituted as described herein.

The term "heteroaryl" refers to refers to a monovalent monocyclic aromatic group and/or multicyclic aromatic group that contain at least one aromatic ring, wherein at least one aromatic ring contains one or more heteroatoms independently selected from O, S, and N in the ring. Heteroaryl groups are bonded to the rest of the molecule through the aromatic ring. Each ring of a heteroaryl group can contain one or two O atoms, one or two S atoms, and/or one to four N atoms, provided that the total number of heteroatoms in each ring is four or less and each ring contains at least one carbon atom. In certain embodiments, the heteroaryl has from 5 to 20, from 5 to 15, or from 5 to 10 ring atoms. Examples of monocyclic heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl, and triazolyl. Examples of bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, benzimidazolyl, benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzotriazolyl, benzoxazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indolizinyl, indolyl, indazolyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinolinyl, quinoxalinyl, quinazolinyl, thiadiazolopyrimidyl, and thienopyridyl. Examples of tricyclic heteroaryl groups include, but are not limited to, acridinyl, benzindolyl, carbazolyl, dibenzofuranyl, perimidinyl, phenanthrolinyl, phenanthridinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, and xanthenyl. In certain embodiments, heteroaryl may also be optionally substituted as described herein.

The term "alkylaryl" refers to an aryl group with an alkyl substituent. The term "aralkyl" or "arylalkyl" includes an alkyl group with an aryl substituent.

The term "alkylheterocyclyl" refers to a heterocyclyl group with an alkyl substituent. The term alkylheterocyclyl includes an alkyl group with a heterocyclyl substituent.

The term "alkylheteroaryl" refers to a heteroaryl group with an alkyl substituent. The term alkylheteroaryl includes an alkyl group with a heteroaryl substituent.

The term "protecting group" as used herein and unless otherwise defined refers to a group that is added to an oxygen, nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis.

"Pharmaceutically acceptable salt" refers to any salt of a compound provided herein which retains its biological properties and which is not toxic or otherwise undesirable for pharmaceutical use. Such salts may be derived from a variety of organic and inorganic counter-ions well known in the art. Such salts include, but are not limited to: (1) acid addition salts formed with organic or inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, sulfamic, acetic, trifluoroacetic, trichloroacetic, propionic, hexanoic, cyclopentylpropionic, glycolic, glutaric, pyruvic, lactic, malonic, succinic, sorbic, ascorbic, malic, maleic, fumaric, tartaric, citric, benzoic, 3-(4-hydroxybenzoyl)benzoic, picric, cinnamic, mandelic, phthalic, lauric, methanesulfonic, ethanesulfonic, 1,2-ethane-disulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, 4-chlorobenzenesulfonic, 2-naphthalenesulfonic, 4-toluenesulfonic, camphoric, camphorsulfonic, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic, glucoheptonic, 3-phenylpropionic, trimethylacetic, tert-butylacetic, lauryl sulfuric, gluconic, benzoic, glutamic, hydroxynaphthoic, salicylic, stearic, cyclohexylsulfamic, quinic, muconic acid and the like acids; or (2) salts formed when an acidic proton present in the parent compound either (a) is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion or an aluminum ion, or alkali metal or alkaline earth metal hydroxides, such as sodium, potassium, calcium, magnesium, aluminum, lithium, zinc, and barium hydroxide, ammonia or (b) coordinates with an organic base, such as aliphatic, alicyclic, or aromatic organic amines, such as ammonia, methylamine, dimethylamine, diethylamine, picoline, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylene-diamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, N-methylglucamine piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

Pharmaceutically acceptable salts further include, by way of example only and without limitation, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium and the like, and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrohalides, e.g. hydrochloride and hydrobromide, sulfate, phosphate, sulfamate, nitrate, acetate, trifluoroacetate, trichloroacetate, propionate, hexanoate, cyclopentylpropionate, glycolate, glutarate, pyruvate, lactate, malonate, succinate, sorbate, ascorbate, malate, maleate, fumarate, tartarate, citrate, benzoate, 3-(4-hydroxybenzoyl)benzoate, picrate, cinnamate, mandelate, phthalate, laurate, methanesulfonate (mesylate), ethanesulfonate, 1,2-ethane-disulfonate, 2-hydroxyethanesulfonate, benzenesulfonate (besylate), 4-chlorobenzenesulfonate, 2-naphthalenesulfonate, 4-toluenesulfonate, camphorate, camphorsulfonate, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylate, glucoheptonate,

3-phenylpropionate, trimethylacetate, tert-butylacetate, lauryl sulfate, gluconate, benzoate, glutamate, hydroxynaphthoate, salicylate, stearate, cyclohexylsulfamate, quinate, muconate and the like.

The term "purine" or "pyrimidine" base refers to, but is not limited to, adenine, N^6-alkylpurines, N^6-acylpurines (wherein acyl is C(O)(alkyl, aryl, alkylaryl, or arylalkyl), N^6-benzylpurine, N^6-halopurine, N^6-vinylpurine, N^6-acetylenic purine, N^6-acyl purine, N^6-hydroxyalkyl purine, N^6-alkylaminopurine, N^6-thioalkyl purine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrmidine, uracil, 5-halouracil, including 5-fluorouracil, C^5-alkylpyrimidines, C^5-benzylpyrimidines, C^5-halopyrimidines, C^5-vinylpyrimidine, C^5-acetylenic pyrimidine, C^5-acyl pyrimidine, C^5-hydroxyalkyl purine, C^5-amidopyrimidine, C^5-cyanopyrimidine, C^5-iodopyrimidine, C^6-iodo-pyrimidine, C^5—Br-vinyl pyrimidine, C^6—Br-vinyl pyrimidine, C^5-nitropyrimidine, C^5-amino-pyrimidine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl. Purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 7-deazaguanine, 7-deazaadenine, 2,6-diaminopurine, and 6-chloropurine. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, t-butyldimethylsilyl, and t-butyldiphenylsilyl, trityl, alkyl groups, and acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

The term "acyl" or "O-linked ester" refers to a group of the formula C(O)R', wherein R' is alkyl or cycloalkyl (including lower alkyl), carboxylate reside of amino acid, aryl including phenyl, alkaryl, arylalkyl including benzyl, alkoxyalkyl including methoxymethyl, aryloxyalkyl such as phenoxymethyl; or substituted alkyl (including lower alkyl), aryl including phenyl optionally substituted with chloro, bromo, fluoro, iodo, C_1 to C_4 alkyl or C_1 to C_4 alkoxy, sulfonate esters such as alkyl or arylalkyl sulphonyl including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl, alkaryl, arylalkyl including benzyl, alkoxyalkyl including methoxymethyl, aryloxyalkyl such as phenoxymethyl. Aryl groups in the esters optimally comprise a phenyl group. In particular, acyl groups include acetyl, trifluoroacetyl, methylacetyl, cyclpropylacetyl, propionyl, butyryl, hexanoyl, heptanoyl, octanoyl, neo-heptanoyl, phenylacetyl, 2-acetoxy-2-phenylacetyl, diphenylacetyl, α-methoxy-α-trifluoromethyl-phenylacetyl, bromoacetyl, 2-nitro-benzeneacetyl, 4-chloro-benzeneacetyl, 2-chloro-2, 2-diphenylacetyl, 2-chloro-2-phenylacetyl, trimethylacetyl, chlorodifluoroacetyl, perfluoroacetyl, fluoroacetyl, bromodifluoroacetyl, methoxyacetyl, 2-thiopheneacetyl, chlorosulfonylacetyl, 3-methoxyphenylacetyl, phenoxyacetyl, tert-butylacetyl, trichloroacetyl, monochloro-acetyl, dichloroacetyl, 7H-dodecafluoro-heptanoyl, perfluoro-heptanoyl, 7H-dodeca-fluoroheptanoyl, 7-chlorododecafluoro-heptanoyl, 7-chloro-dodecafluoro-heptanoyl, 7H-dodecafluoro-heptanoyl, 7H-dodeca-fluoroheptanoyl, nona-fluoro-3,6-dioxa-heptanoyl, nonafluoro-3,6-dioxaheptanoyl, perfluoroheptanoyl, methoxybenzoyl, methyl 3-amino-5-phenylthiophene-2-carboxyl, 3,6-dichloro-2-methoxy-benzoyl, 4-(1,1,2,2-tetrafluoro-ethoxy)-benzoyl, 2-bromo-propionyl, omega-aminocapryl, decanoyl, n-pentadecanoyl, stearyl, 3-cyclopentyl-propionyl, 1-benzene-carboxyl, O-acetylmandelyl, pivaloyl acetyl, 1-adamantane-carboxyl, cyclohexane-carboxyl, 2,6-pyridinedicarboxyl, cyclopropane-carboxyl, cyclobutane-carboxyl, perfluorocyclohexyl carboxyl, 4-methylbenzoyl, chloromethyl isoxazolyl carbonyl, perfluorocyclohexyl carboxyl, crotonyl, 1-methyl-1H-indazole-3-carbonyl, 2-propenyl, isovaleryl, 1-pyrrolidinecarbonyl, 4-phenylbenzoyl.

The term "amino acid" refers to naturally occurring and synthetic α, β γ or δ amino acids, and includes but is not limited to, amino acids found in proteins, i.e. glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine. In certain embodiments, the amino acid is in the L-configuration. Alternatively, the amino acid can be a derivative of alanyl, valinyl, leucinyl, isoleuccinyl, prolinyl, phenylalaninyl, tryptophanyl, methioninyl, glycinyl, serinyl, threoninyl, cysteinyl, tyrosinyl, asparaginyl, glutaminyl, aspartoyl, glutaroyl, lysinyl, argininyl, histidinyl, β-alanyl, β-valinyl, β-leucinyl, β-isoleuccinyl, β-prolinyl, β-phenylalaninyl, β-tryptophanyl, β-methioninyl, β-glycinyl, β-serinyl, β-threoninyl, β-cysteinyl, β-tyrosinyl, β-asparaginyl, β-glutaminyl, β-aspartoyl, β-glutaroyl, β-lysinyl, β-argininyl or β-histidinyl.

The term "amino acid derivative" refers to a group derivable from a naturally or non-naturally occurring amino acid, as described and exemplified herein. Amino acid derivatives are apparent to those of skill in the art and include, but are not limited to, ester, amino alcohol, amino aldehyde, amino lactone, and N-methyl derivatives of naturally and non-naturally occurring amino acids. In an embodiment, an amino acid derivative is provided as a substituent of a compound described herein, wherein the substituent is —NH-G(S_C)—C(O)-Q or —OC(O)G(S_C)-Q, wherein Q is —SR, —NRR or alkoxyl, R is hydrogen or alkyl, S_C is a side chain of a naturally occurring or non-naturally occurring amino acid and G is C_1-C_2 alkyl. In certain embodiments, G is C_1 alkyl and S_C is selected from the group consisting of hydrogen, alkyl, heteroalkyl, arylalkyl and heteroarylalkyl.

The term "substantially free of" or "substantially in the absence of" with respect to a nucleoside composition refers to a nucleoside composition that includes at least 85 or 90% by weight, in certain embodiments 95%, 98%, 99% or 100% by weight, of the designated enantiomer of that nucleoside. In certain embodiments, in the methods and compounds provided herein, the compounds are substantially free of enantiomers.

Similarly, the term "isolated" with respect to a nucleoside composition refers to a nucleoside composition that includes at least 85, 90%, 95%, 98%, 99% to 100% by weight, of the nucleoside, the remainder comprising other chemical species or enantiomers.

"Solvate" refers to a compound provided herein or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

"Isotopic composition" refers to the amount of each isotope present for a given atom, and "natural isotopic composition" refers to the naturally occurring isotopic composition or abundance for a given atom. Atoms containing their natural isotopic composition may also be referred to herein as "non-enriched" atoms. Unless otherwise designated, the atoms of the compounds recited herein are meant to represent any stable isotope of that atom. For example, unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural isotopic composition.

"Isotopic enrichment" refers to the percentage of incorporation of an amount of a specific isotope at a given atom in a molecule in the place of that atom's natural isotopic abundance. For example, deuterium enrichment of 1% at a given position means that 1% of the molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The isotopic enrichment of the compounds provided herein can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

"Isotopically enriched" refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom.

As used herein, "alkyl," "cycloalkyl," "alkenyl," "cycloalkenyl," "alkynyl," "aryl," "alkoxy," "alkoxycarbonyl," "amino," "carboxyl," "alkylamino," "arylamino," "thioalkyoxy," "heterocyclyl," "heteroaryl," "alkylheterocyclyl," "alkylheteroaryl," "acyl," "aralkyl," "alkaryl," "purine," "pyrimidine," "carboxyl" and "amino acid" groups optionally comprise deuterium at one or more positions where hydrogen atoms are present, and wherein the deuterium composition of the atom or atoms is other than the natural isotopic composition.

Also as used herein, "alkyl," "cycloalkyl," "alkenyl," "cycloalkenyl," "alkynyl," "aryl," "alkoxy," "alkoxycarbonyl," "carboxyl," "alkylamino," "arylamino," "thioalkyoxy," "heterocyclyl," "hetero aryl," "alkylheterocyclyl," "alkylheteroaryl," "acyl," "aralkyl," "alkaryl," "purine," "pyrimidine," "carboxyl" and "amino acid" groups optionally comprise carbon-13 at an amount other than the natural isotopic composition.

As used herein, EC_{50} refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

As used herein, the IC_{50} refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response in an assay that measures such response.

The term "host", as used herein, refers to any unicellular or multicellular organism in which the virus can replicate, including cell lines and animals, and in certain embodiments, a human. Alternatively, the host can be carrying a part of the Flaviviridae viral genome, whose replication or function can be altered by the compounds of the present invention. The term host specifically includes infected cells, cells transfected with all or part of the Flaviviridae genome and animals, in particular, primates (including chimpanzees) and humans. In most animal applications of the present invention, the host is a human patient. Veterinary applications, in certain indications, however, are clearly anticipated by the present invention (such as chimpanzees).

As used herein, the terms "subject" and "patient" are used interchangeably herein. The terms "subject" and "subjects" refer to an animal, such as a mammal including a non-primate (e.g., a cow, pig, horse, cat, dog, rat, and mouse) and a primate (e.g., a monkey such as a cynomolgous monkey, a chimpanzee and a human), and for example, a human. In certain embodiments, the subject is refractory or non-responsive to current treatments for hepatitis C infection. In another embodiment, the subject is a farm animal (e.g., a horse, a cow, a pig, etc.) or a pet (e.g., a dog or a cat). In certain embodiments, the subject is a human.

As used herein, the terms "therapeutic agent" and "therapeutic agents" refer to any agent(s) which can be used in the treatment or prevention of a disorder or one or more symptoms thereof. In certain embodiments, the term "therapeutic agent" includes a compound provided herein. In certain embodiments, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the treatment or prevention of a disorder or one or more symptoms thereof.

"Therapeutically effective amount" refers to an amount of a compound or composition that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. A "therapeutically effective amount" can vary depending on, inter alia, the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated.

"Treating" or "treatment" of any disease or disorder refers, in certain embodiments, to ameliorating a disease or disorder that exists in a subject. In another embodiment, "treating" or "treatment" includes ameliorating at least one physical parameter, which may be indiscernible by the subject. In yet another embodiment, "treating" or "treatment" includes modulating the disease or disorder, either physically (e.g., stabilization of a discernible symptom) or physiologically (e.g., stabilization of a physical parameter) or both. In yet another embodiment, "treating" or "treatment" includes delaying the onset of the disease or disorder.

As used herein, the terms "prophylactic agent" and "prophylactic agents" as used refer to any agent(s) which can be used in the prevention of a disorder or one or more symptoms thereof. In certain embodiments, the term "prophylactic agent" includes a compound provided herein. In certain other embodiments, the term "prophylactic agent" does not refer a compound provided herein. For example, a prophylactic agent is an agent which is known to be useful for, or has been or is currently being used to prevent or impede the onset, development, progression and/or severity of a disorder.

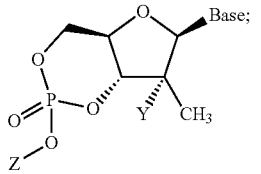
As used herein, the phrase "prophylactically effective amount" refers to the amount of a therapy (e.g., prophylactic agent) which is sufficient to result in the prevention or reduction of the development, recurrence or onset of one or more symptoms associated with a disorder, or to enhance or improve the prophylactic effect(s) of another therapy (e.g., another prophylactic agent).

Compounds

Provided herein are 3',5'-cyclic phosphate prodrug compounds useful for the treatment of Flaviviridae infections such as HCV infection. The 3',5'-cyclic phosphate prodrug compounds can be formed as described herein and used for the treatment of Flaviviridae infections such as HCV infection.

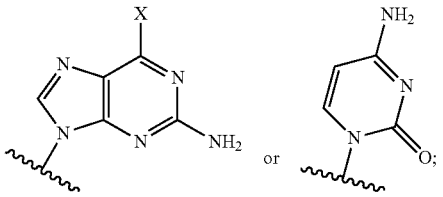
In certain embodiments, provided herein are compounds of Formula (VIII):

(VIII)

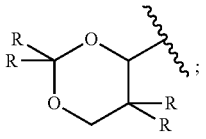


or a pharmaceutically acceptable salt, solvate, stereoisomeric form, tautomeric form or polymorphic form thereof, wherein:

each Base is independently

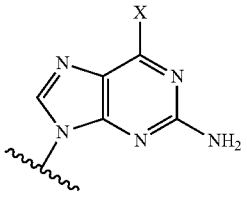


each X is independently alkoxyl, hydrogen, or hydroxyl; each Y is independently hydroxyl, acetoxyl, or fluoro; each Z is independently -LC(O)O(L)$_p$CR$_3$, -L-Ar—C(O)O(L)$_p$CR$_3$, —CR(E)(L)$_p$OC(O)O(L)$_p$CR$_3$, -LSC(O)LOH, -LSC(O)LOC(O)(L)$_p$CR$_3$, -LSC(O)LOC(O)(L)$_p$NR$_2$, -LS-S(L)$_p$CR$_3$, -LS-SLOH, -LNRC(O)O(L)$_p$CR$_3$, -LSC(O)LNRC(O)O(L)$_p$CR$_3$, —Ar—B, -L-B, -LNRC(O)D, -LNRC(O)CH(OH)(CR$_2$)$_2$OH, or -(L)$_p$CR(R^A)C(O)O(L)$_p$CR$_3$; each B is independently an alkyl group substituted with aminocarboxylene, carboxylene, or both; each D is independently

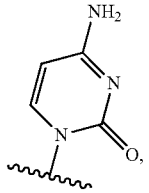


each E is independently alkyl, substituted alkyl, aryl, or heteroaryl; each Ar is independently an arylene or heteroarylene; each L is independently alkylene or substituted alkylene; each R is independently hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl; each R^A is independently a carbocyclic or heterocyclic ring; and each p is independently 0 or 1. All combinations of such embodiments are within the scope of this disclosure.

Tautomeric forms of the compounds described herein are within the scope of this disclosure. For example: when Base is

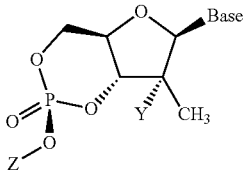


and X is hydroxyl, the corresponding carbonyl tautomer is within the scope of this disclosure; and when Base

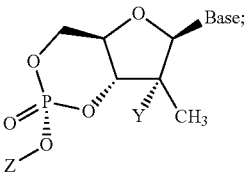


is the corresponding imino tautomer is within the scope of this disclosure.

In certain embodiments, provided herein are compounds of Formula (VIIIa) or (VIIIb):



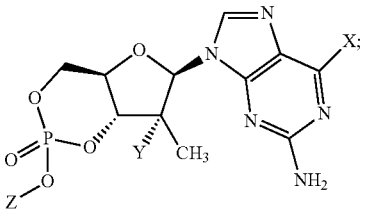
(VIIIa)



(VIIIb)

or pharmaceutically acceptable salts, solvates, stereoisomeric forms, tautomeric forms or polymorphic forms thereof, wherein each of Y and Z are as described in the context of Formula (VIII).

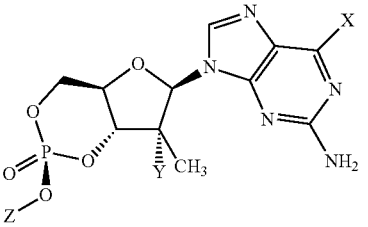
In certain embodiments, provided herein are compounds according to Formula I:



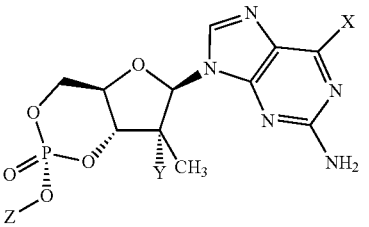
(I)

or pharmaceutically acceptable salts, solvates, stereoisomeric forms, tautomeric forms or polymorphic forms thereof, wherein each X is independently alkoxyl, hydrogen, or hydroxyl and Y and Z are as described in the context of Formula (VIII).

In certain embodiments, provided herein are compounds according to formula Ia or Ib:



(Ia)

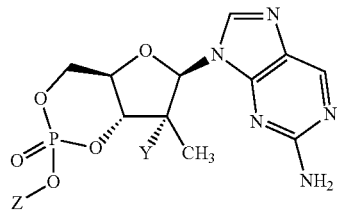


(Ib)

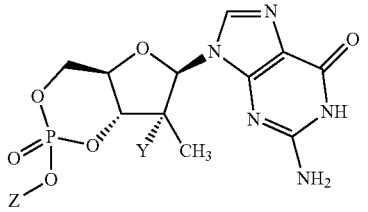
or pharmaceutically acceptable salts, solvates, stereoisomeric forms, tautomeric forms or polymorphic forms thereof, wherein X, Y, and Z are as defined in the context of Formula VIII.

In certain embodiments, provided herein are compounds according to any of formulas II, III, or IV:

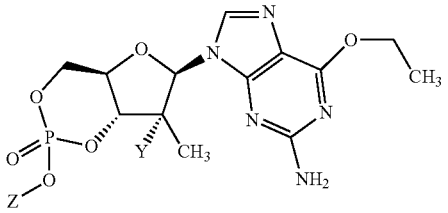
(II)



(III)



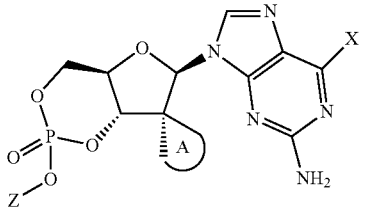
(IV)



or pharmaceutically acceptable salts, solvates, stereoisomeric forms, tautomeric forms or polymorphic forms thereof, wherein Y and Z are as defined in the context of Formula VIII. In certain embodiments, each Y is independently hydroxyl or fluoro. In certain embodiments, each Y is hydroxyl. In certain embodiments, each Y is fluoro.

In certain embodiments, a compound of Formula V is provided:

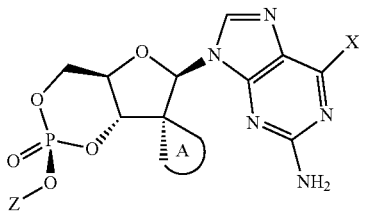
(V)



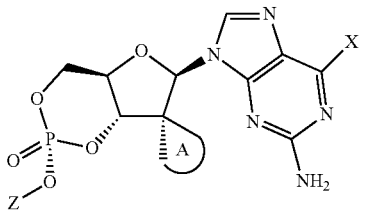
or pharmaceutically acceptable salts, solvates, stereoisomeric forms, tautomeric forms or polymorphic forms thereof, wherein: each X is independently alkoxyl, hydrogen, or hydroxyl; or each X is as defined in the context of Formula VIII; each ring A is independently a 3-10 membered carbocyclic or heterocyclic ring; and each Z is independently alkyl, substituted alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, or a combination thereof; or each Z is as defined in the context of Formula VIII. In certain embodiments, ring A is oxacyclopropyl or oxacyclobutyl.

In certain embodiments, a compound of Formula Va or Vb is provided:

(Va)



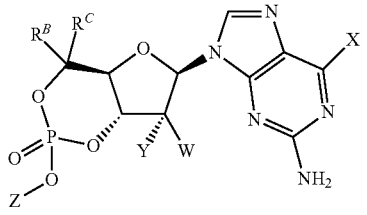
(Vb)



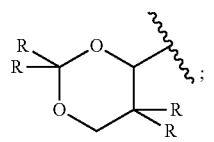
or pharmaceutically acceptable salts, solvates, stereoisomeric forms, tautomeric forms or polymorphic forms thereof, wherein ring A, X, Y, and Z are as defined in the context of Formula VI; or X, Y, and Z are as defined in the context of Formula VIII.

In certain embodiments, a compound of Formula VI is provided:

(VI)



or pharmaceutically acceptable salts, solvates, stereoisomeric forms, tautomeric forms or polymorphic forms thereof, wherein: each X is independently alkoxyl, hydrogen, or hydroxyl; each Y is independently hydroxyl, acetoxyl, or fluoro; each W is independently hydrogen, fluoro, or methyl; each Z is independently -LC(O)O(L)$_p$CR$_3$, -L-Ar—C(O)O(L)$_p$CR$_3$, —CR(E)(L)$_p$OC(O)O(L)$_p$CR$_3$, -LSC(O)LOH, -LSC(O)LOC(O)(L)$_p$CR$_3$, -LS-S(L)$_p$CR$_3$, -LS-SLOH, -LNRC(O)O(L)$_p$CR$_3$, —Ar—B, -L-B, -LNRC(O)D, -LNRC(O)CH(OH)(CR$_2$)$_2$OH, or -(L)$_p$CR(R^A)C(O)O(L)$_p$CR$_3$; each B is independently an alkyl group substituted with aminocarboxylene, carboxylene, or both; each D is independently



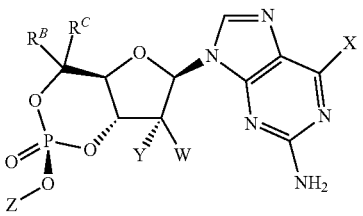
each E is independently alkyl, substituted alkyl, aryl, or heteroaryl; each Ar is independently an arylene or heteroarylene; each L is independently alkylene, or substituted alkylene; each R is independently hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl; each R^A is independently a carbocyclic or heterocyclic ring; each p is independently 0 or 1; and each of

R^B and R^C is independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_5-C_{10} aryl, or C_5-C_{10} heteroaryl; or R^B and R^C are each independently selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl and an optionally substituted C_{1-6} haloalkyl, and optionally at least one of R^B and R^C is not hydrogen; or R^B and R^C are taken together to form a group selected from among C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{3-6} aryl, and C_{3-6} heteroaryl. In certain embodiments, each R^B and R^C is independently hydrogen or methyl. In certain embodiments, each R^B and R^C is hydrogen. In certain embodiments, each R^B and R^C is methyl. In certain embodiments, each R^B is hydrogen and each R^C is methyl.

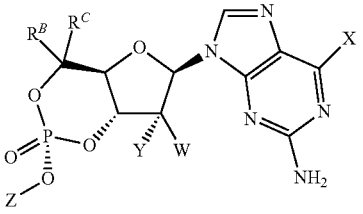
In certain embodiments, each W is independently hydrogen. In certain embodiments, each W is independently fluoro. In certain embodiments, each W is independently methyl.

In certain embodiments, a compound of Formula VIa or VIb is provided:

(VIa)



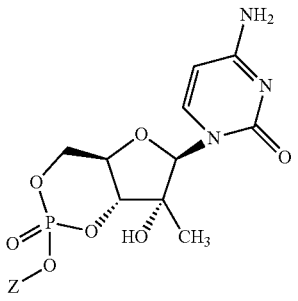
(VIb)



or pharmaceutically acceptable salts, solvates, stereoisomeric forms, tautomeric forms or polymorphic forms thereof, wherein: each of W, X, Y, Z, R^B and R^C are as defined herein in the context of Formula VI.

In certain embodiments, a compound of Formula (IX) is provided:

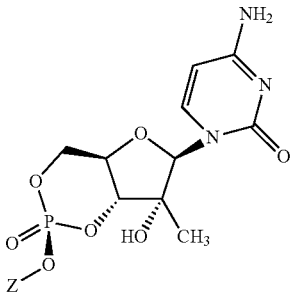
(IX)



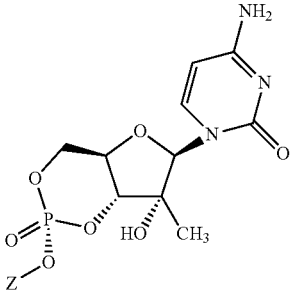
or a pharmaceutically acceptable salt, solvate, stereoisomeric form, tautomeric form or polymorphic form thereof, wherein: each Z is independently -LSC(O)LC(O)O(L)$_p$CR$_3$ or -LSC(O)LNRC(O)O(L)$_p$CR$_3$; each L is independently alkylene or substituted alkylene; each R is independently hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl; and each p is independently 0 or 1.

In certain embodiments, a compound of any of Formula (IXa) or (IXb) is provided:

(IXa)



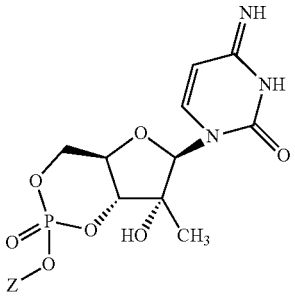
(IXb)



or a pharmaceutically acceptable salt, solvate, stereoisomeric form, tautomeric form or polymorphic form thereof, wherein each Z is as described in the context of Formula (IX).

In certain embodiments, a compound of Formula (IXc) is provided:

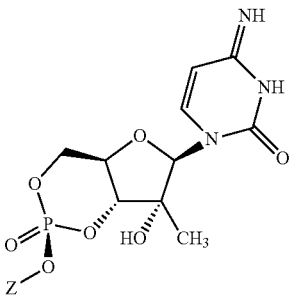
(IXc)



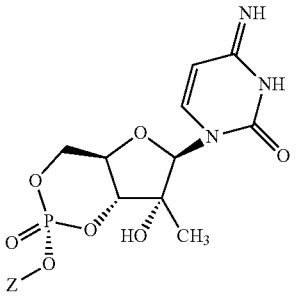
or a pharmaceutically acceptable salt, solvate, stereoisomeric form, tautomeric form or polymorphic form thereof, wherein each Z is as described in the context of Formula (IX).

In certain embodiments, a compound of any of Formula (IXd) or (IXe) is provided:

(IXd)



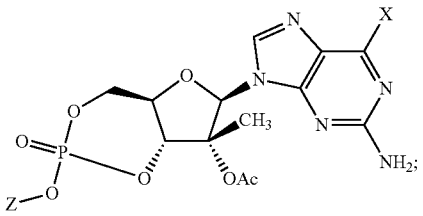
(IXe)



or a pharmaceutically acceptable salt, solvate, stereoisomeric form, tautomeric form or polymorphic form thereof, wherein each Z is as described in the context of Formula (IX).

In certain embodiments, a compound of Formula (X) is provided:

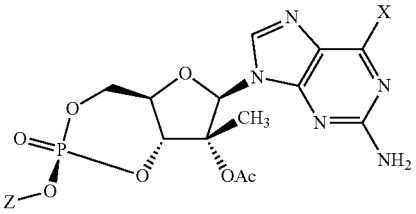
(X)



or a pharmaceutically acceptable salt, solvate, stereoisomeric form, tautomeric form or polymorphic form thereof, wherein each Z is as described in the context of Formula (VIII).

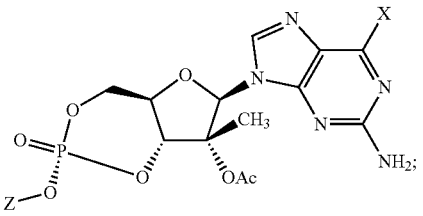
In certain embodiments, a compound of any of Formula (Xa) or (Xb) is provided:

(Xa)



-continued

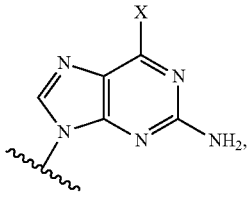
(Xb)



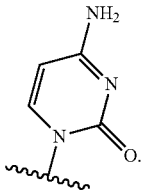
or a pharmaceutically acceptable salt, solvate, stereoisomeric form, tautomeric form or polymorphic form thereof, wherein each Z is as described in the context of Formula (VIII).

In certain embodiments, each Z is independently -LSC(O)$LC(O)O(L)_pCR_3$; where L, R, and p are as defined in the context of Formula (IX). In certain embodiments, each Z is independently -LSC(O)LNRC(O)$O(L)_pCR_3$; where L, R, and p are as defined in the context of Formula (IX).

In certain embodiments, each Base is



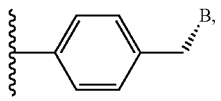
were X is as defined in the context of Formula VIII. In certain embodiments, each Base is



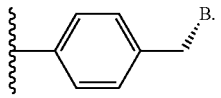
In certain embodiments, each X is independently C_1-C_{10} alkoxyl, hydrogen, or hydroxyl. In certain embodiments, each X is independently C_1-C_5 alkoxyl. In certain embodiments, each X is independently C_1-C_2 alkoxyl. In certain embodiments, each X is methoxyl. In certain embodiments, each X is ethoxyl.

In certain embodiments, each L is independently C_1-C_{10} alkylene or C_1-C_{10} substituted alkylene. In certain embodiments, each L is independently C_1-C_5 alkylene or C_1-C_5 substituted alkylene. In certain embodiments, each L is independently C_1-C_{10} alkylene. In certain embodiments, each L is independently C_1-C_{10} substituted alkylene.

In certain embodiments, each Z is independently —$(CR_2)_m$ $C(O)O(CR_2)_nCR_3$, —$(CR_2)_m$Ar$C(O)O(CR_2)_nCR_3$, —CR(E) $(CR_2)_nOC(O)O(CR_2)_nCR_3$, —$(CR_2)_mSC(O)(CR_2)_mOH$, —$(CR_2)_mSC(O)(CR_2)_mOC(O)(CR_2)_nCR_3$, —$(CR_2)_mS$—S $(CR_2)_nCR_3$, —$(CR_2)_mS$—$S(CR_2)_mOH$, —$(CR_2)_mNRC(O)O$ $(CR_2)_nCR_3$,



—$(CR_2)_nB$, —$(CR_2)_mNRC(O)D$, —$(CR_2)_mNRC(O)CH(OH)(CR_2)_2OH$, or —$(CR_2)_nCR(R^A)C(O)O(CR_2)_nCR_3$; wherein Ar, E, B, D, R, and R^A are as described herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10. In certain embodiments, each Z is independently —$(CR_2)_mC(O)O(CR_2)_nCR_3$. In certain embodiments, each Z is independently —$(CR_2)_mArC(O)O(CR_2)_nCR_3$. In certain embodiments, each Z is independently —$CR(E)(CR_2)_nOC(O)O(CR_2)_nCR_3$. In certain embodiments, each Z is independently —$(CR_2)_mSC(O)(CR_2)_mOH$. In certain embodiments, each Z is independently —$(CR_2)_mSC(O)(CR_2)_mOC(O)(CR_2)_nCR_3$. In certain embodiments, each Z is independently —$(CR_2)_mS—S(CR_2)_nCR_3$. In certain embodiments, each Z is independently —$(CR_2)_mS—S(CR_2)_mOH$. In certain embodiments, each Z is independently —$(CR_2)_mNRC(O)O(CR_2)_nCR_3$. In certain embodiments, each Z is independently



In certain embodiments, each Z is independently —$(CR_2)_nB$. In certain embodiments, each Z is independently —$(CR_2)_mNRC(O)D$. In certain embodiments, each Z is independently —$(CR_2)_mNRC(O)CH(OH)(CR_2)_2OH$. In certain embodiments, each Z is independently —$(CR_2)_nCR(R^A)C(O)O(CR_2)_nCR_3$.

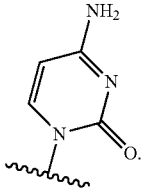
In certain embodiments, each E is independently C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_5-C_{10} aryl, or C_5-C_{10} heteroaryl. In certain embodiments, each E is independently C_1-C_{10} alkyl. In certain embodiments, each E is independently C_1-C_{10} substituted alkyl. In certain embodiments, each E is independently C_5-C_{10} aryl. In certain embodiments, each E is independently C_5-C_{10} heteroaryl.

In certain embodiments, each Ar is independently C_5-C_{10} arylene or C_5-C_{10} heteroarylene. In certain embodiments, each Ar is independently C_5-C_{10} arylene. In certain embodiments, each Ar is independently C_5-C_{10} heteroarylene.

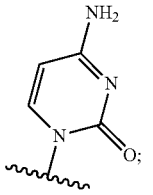
In certain embodiments, each R is independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_5-C_{10} aryl, or C_5-C_{10} heteroaryl. In certain embodiments, each R is independently hydrogen, C_1-C_5 alkyl, C_1-C_5 substituted alkyl, C_5-C_{10} aryl, or C_5-C_{10} heteroaryl. In certain embodiments, each R is independently hydrogen, fluoro, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_5-C_{10} aryl, or C_5-C_{10} heteroaryl.

In certain embodiments, each R^A is independently a 3-20 membered carbocyclic or heterocyclic ring. In certain embodiments, each R^A is independently a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl group. In certain embodiments, each R^A is independently an oxiranyl, oxetanyl, furanyl, oxanyl, or oxepanyl group. In certain embodiments, each R^A is independently an aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, or azepinyl group. In certain embodiments, each R^A is independently a thiiranyl, thietanyl, thiofanyl, thianyl, or thiepanyl group.

In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl and each Base is

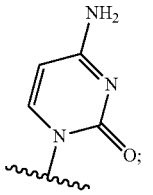


In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is

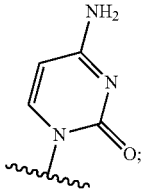


and each Z is —$(CR_2)_mC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is

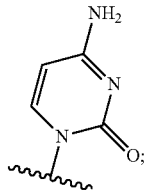


and each Z is —$(CR_2)_mArC(O)O(CR_2)_nCR_3$; wherein R and Ar are as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is

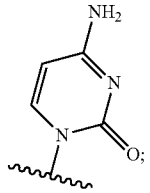


and each Z is —$CR(E)(CR_2)_nOC(O)O(CR_2)_nCR_3$; wherein R and E are as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is

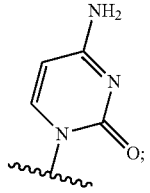


and each Z is —$(CR_2)_mSC(O)(CR_2)_mOH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is



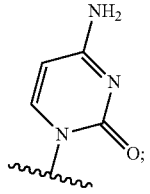
and each Z is —$(CR_2)_mSC(O)(CR_2)_mOC(O)(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is

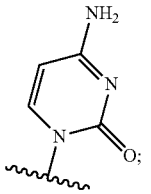


and each Z is —$(CR_2)_mS$—$S(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is

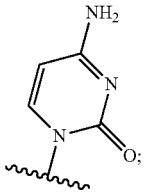


and each Z is —$(CR_2)_mS$—$S(CR_2)_mOH$ wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is

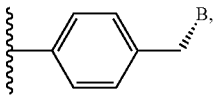


and each Z is —$(CR_2)_mNRC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

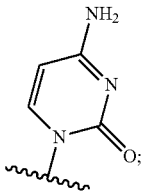
In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is



and each Z is

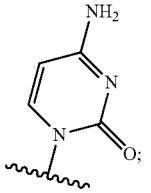


wherein B is as defined in the context of Formula VIII. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is



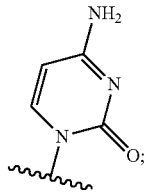
and each Z is —$(CR_2)_nB$, wherein R and B are as defined in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is

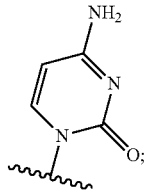


and each Z is —$(CR_2)_mNRC(O)D$; wherein R and D are as defined herein in the context of Formula VIII; and each m is

independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is

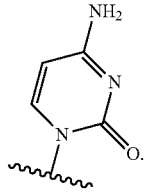


and each Z is —$(CR_2)_m$NRC(O)CH(OH)$(CR_2)_2$OH; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; Base is

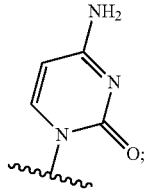


and each Z is —$(CR_2)_n$CR(R^A)C(O)O$(CR_2)_n$$CR_3$; wherein R is as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is fluoro. In certain embodiments, Y is acetoxyl. In certain embodiments, Y is hydroxyl. In certain embodiments, Y is fluoro and each Base is

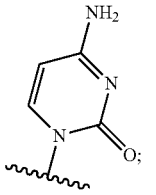


In certain embodiments, Y is fluoro; each Base is

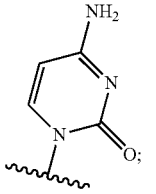


and each Z is —$(CR_2)_m$C(O)O(CR_2)—CR_3; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is fluoro; each Base is

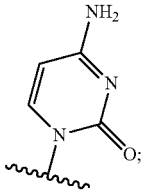


and each Z is —$(CR_2)_m$ArC(O)O(CR_2)—CR_3; wherein R and Ar are as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10. In certain embodiments, Y is fluoro; each Base is

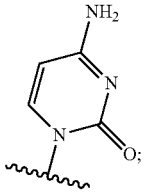


and each Z is —CR(E)$(CR_2)_n$OC(O)O$(CR_2)_n$$CR_3$; wherein R and E are as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is fluoro; each Base is

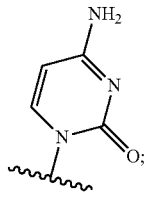


and each Z is —$(CR_2)_m$SC(O)$(CR_2)_m$OH; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is fluoro; each Base is



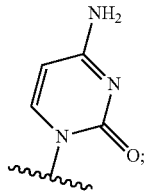
and each Z is —$(CR_2)_m$SC(O)$(CR_2)_m$OC(O)$(CR_2)_n$$CR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is fluoro; each Base is

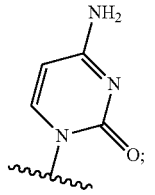


and each Z is —$(CR_2)_mS$—$S(CR_2)$—CR_3; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is fluoro; each Base is

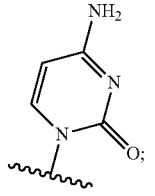


and each Z is —$(CR_2)_mS$—$S(CR_2)_mOH$ wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is fluoro; each Base is

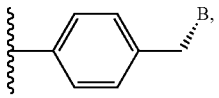


and each Z is —$(CR_2)_mNRC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

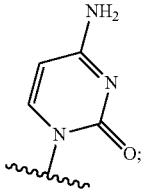
In certain embodiments, Y is fluoro; each Base is



and each Z is

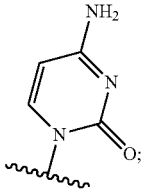


wherein B is as defined in the context of Formula VIII. In certain embodiments, Y is fluoro; each Base is

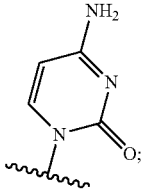


and each Z is —$(CR_2)_nB$, wherein R and B are as defined in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

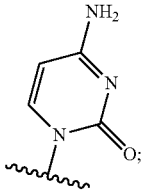
In certain embodiments, Y is fluoro; each Base is



and each Z is —$(CR_2)_mNRC(O)D$; wherein R and D are as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is fluoro; each Base is

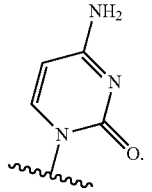


and each Z is —$(CR_2)_mNRC(O)CH(OH)(CR_2)_2OH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is fluoro; each Base is

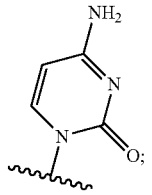


and each Z is —$(CR_2)_nCR(R^A)C(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is acetoxyl and each Base is

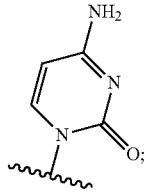


In certain embodiments, Y is acetoxyl; each Base is

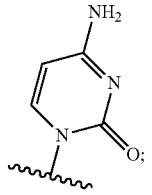


and each Z is —$(CR_2)_mC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is acetoxyl; each Base is

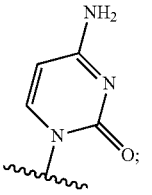


and each Z is —$(CR_2)_mArC(O)O(CR_2)$—CR_3; wherein R and Ar are as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10. In certain embodiments, Y is acetoxyl; each Base is

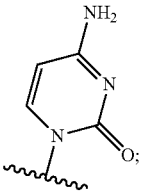


and each Z is —$CR(E)(CR_2)_nOC(O)O(CR_2)_nCR_3$; wherein R and E are as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is acetoxyl; each Base is

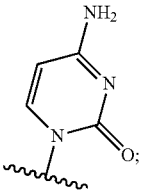


and each Z is —$(CR_2)_mSC(O)(CR_2)_mOH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is acetoxyl; each Base is



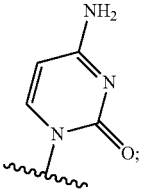
and each Z is —$(CR_2)_mSC(O)(CR_2)_mOC(O)(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is acetoxyl; each Base is

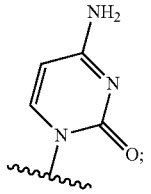


and each Z is —$(CR_2)_mS$—$S(CR_2)$—CR_3; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is acetoxyl; each Base is

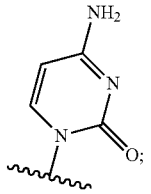


and each Z is —$(CR_2)_mS$—$S(CR_2)_mOH$ wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is acetoxyl; each Base is

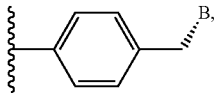


and each Z is —$(CR_2)_m$NRC(O)O$(CR_2)_n CR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

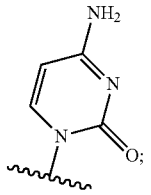
In certain embodiments, Y is acetoxyl; each Base is



and each Z is

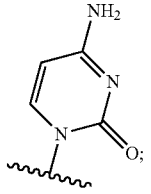


wherein B is as defined in the context of Formula VIII. In certain embodiments, Y is acetoxyl; each Base is

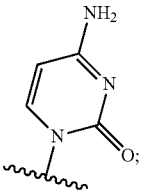


and each Z is —$(CR_2)_n$B, wherein R and B are as defined in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

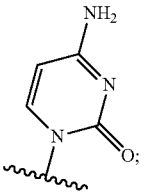
In certain embodiments, Y is acetoxyl; each Base is



and each Z is —$(CR_2)_m$NRC(O)D; wherein R and D are as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is acetoxyl; each Base is

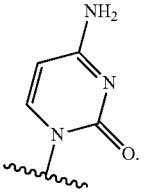


and each Z is —$(CR_2)_m$NRC(O)CH(OH)$(CR_2)_2$OH; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is acetoxyl; each Base is

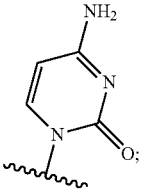


and each Z is —$(CR_2)_n CR(R^A)C(O)O(CR_2)_n CR_3$; wherein R is as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is hydroxyl and each Base is

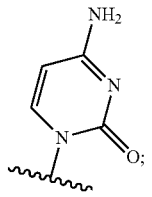


In certain embodiments, Y is hydroxyl; each Base is

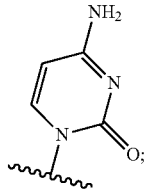


and each Z is —$(CR_2)_m C(O)O(CR_2)_n CR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is hydroxyl; each Base is

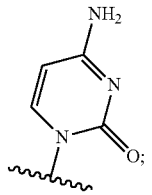


and each Z is —$(CR_2)_m$ArC(O)O(CR_2)—CR_3; wherein R and Ar are as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10. In certain embodiments, Y is hydroxyl; each Base is

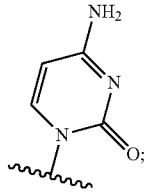


and each Z is —$CR(E)(CR_2)_n$OC(O)O$(CR_2)_n CR_3$; wherein R and E are as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is hydroxyl; each Base is

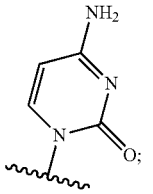


and each Z is —$(CR_2)_m$SC(O)$(CR_2)_m$OH; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is hydroxyl; each Base is



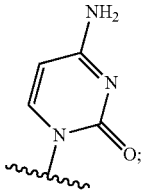
and each Z is —$(CR_2)_m$SC(O)$(CR_2)_m$OC(O)$(CR_2)_n CR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is hydroxyl; each Base is

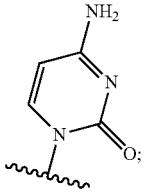


and each Z is —$(CR_2)_m$S—S(CR_2)—CR_3; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is hydroxyl; each Base is

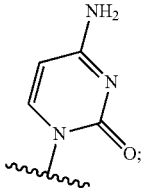


and each Z is —$(CR_2)_m$S—S$(CR_2)_m$OH wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is hydroxyl; each Base is

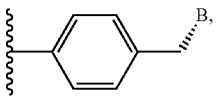


and each Z is —$(CR_2)_m$NRC(O)O$(CR_2)_n CR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Y is hydroxyl; each Base is

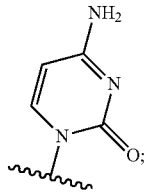


and each Z is



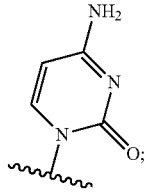
wherein B is as defined in the context of Formula VIII. In certain

embodiments, Y is hydroxyl; each Base is

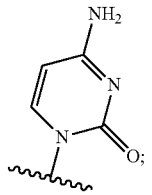


and each Z is —$(CR_2)_nB$, wherein R and B are as defined in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

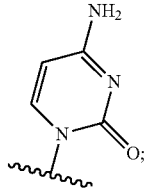
In certain embodiments, Y is hydroxyl; each Base is



and each Z is —$(CR_2)_mNRC(O)D$; wherein R and D are as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is hydroxyl; each Base is

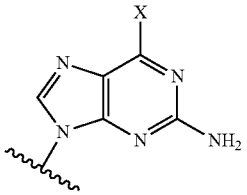


and each Z is —$(CR_2)_mNRC(O)CH(OH)(CR_2)_2OH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is hydroxyl; each Base is

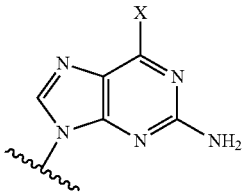


and each Z is —$(CR_2)_nCR(R^A)C(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

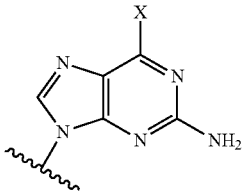
In certain embodiments, Base is



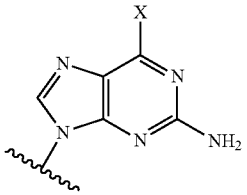
and X is C_1-C_{10} alkoxyl. In certain embodiments, Base is



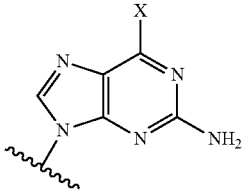
and X is hydroxyl. In certain embodiments, Base is



and X is hydrogen. In certain embodiments, Base is

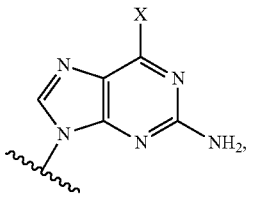


and X is methoxyl. In certain embodiments, Base is



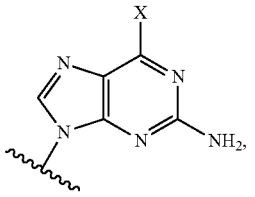
and X is ethoxyl.

In certain embodiments, Base is



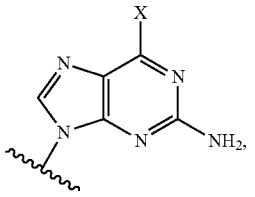
each Y is independently fluoro, acetoxyl, or hydroxyl and X is hydrogen. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is $—(CR_2)_mC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



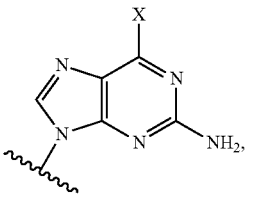
each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is $—(CR_2)_mArC(O)O(CR_2)_nCR_3$; wherein R and Ar are as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is $—CR(E)(CR_2)_nOC(O)O(CR_2)_nCR_3$; wherein R and E are as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



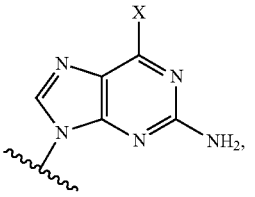
each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is $—(CR_2)_mSC(O)(CR_2)_mOH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is $—(CR_2)_mSC(O)(CR_2)_mOC(O)(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



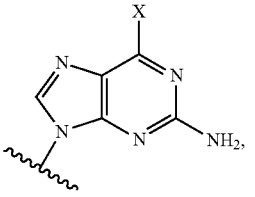
each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is $—(CR_2)_mS—S(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

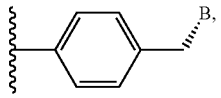


each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is $—(CR_2)_mS—S(CR_2)_mOH$ wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is $—(CR_2)_mNRC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

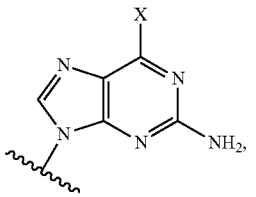


each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is



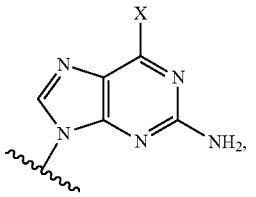
wherein B is as defined in the context of Formula VIII. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is $—(CR_2)_nB$, wherein R and B are as defined in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



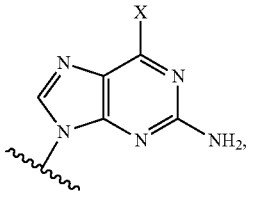
each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is $—(CR_2)_mNRC(O)D$; wherein R and D are as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is $—(CR_2)_mNRC(O)CH(OH)(CR_2)_2OH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydrogen; and each Z is $—(CR_2)_n CR(R^4)C(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



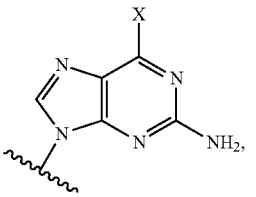
each Y is independently fluoro, acetoxyl, or hydroxyl and X is hydroxyl. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is $—(CR_2)_mC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



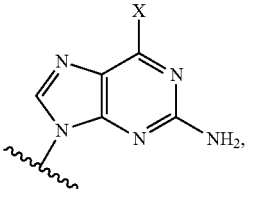
each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is $—(CR_2)_mArC(O)O(CR_2)_nCR_3$; wherein R and Ar are as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is $—CR(E)(CR_2)_nOC(O)O(CR_2)_n CR_3$; wherein R and E are as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



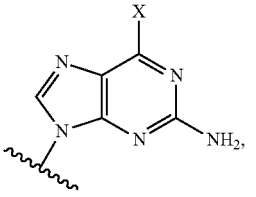
each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is $—(CR_2)_mSC(O)(CR_2)_mOH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is $—(CR_2)_m SC(O)(CR_2)_mOC(O)(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



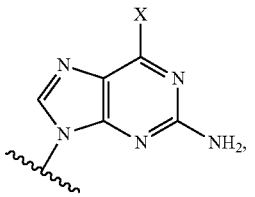
each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is $—(CR_2)_mS—S(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

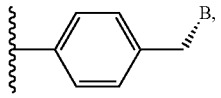


each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is $—(CR_2)_mS—S(CR_2)_mOH$ wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is $—(CR_2)_m NRC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

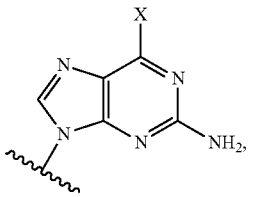


each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is



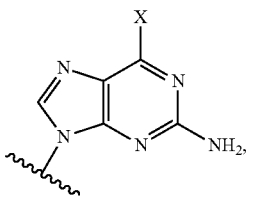
wherein B is as defined in the context of Formula VIII. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is $—(CR_2)_n$ B, wherein R and B are as defined in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



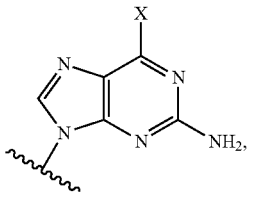
each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is $—(CR_2)_mNRC(O)D$; wherein R and D are as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is $—(CR_2)_mNRC(O)CH(OH)(CR_2)_2OH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is hydroxyl; and each Z is $—(CR_2)_n CR(R^4)C(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



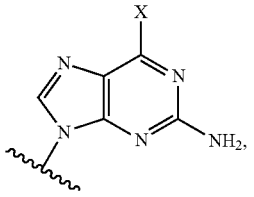
each Y is independently fluoro, acetoxyl, or hydroxyl and X is methoxyl. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is $—(CR_2)_mC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



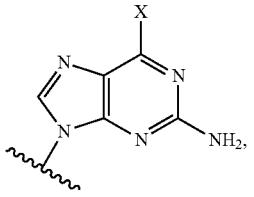
each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is $—(CR_2)_mArC(O)O(CR_2)_nCR_3$; wherein R and Ar are as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is $—CR(E)(CR_2)_nOC(O)O(CR_2)_n CR_3$; wherein R and E are as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



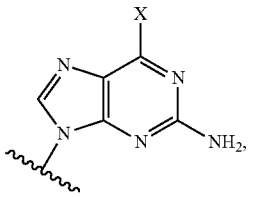
each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is $—(CR_2)_mSC(O)(CR_2)_mOH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is $—(CR_2)_m SC(O)(CR_2)_mOC(O)(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



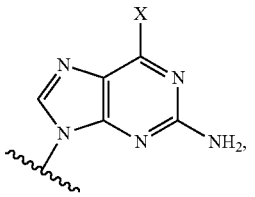
each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is $—(CR_2)_mS—S(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

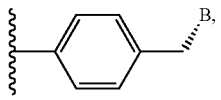


each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is —$(CR_2)_mS$—$S(CR_2)_mOH$ wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is —$(CR_2)_m$ $NRC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

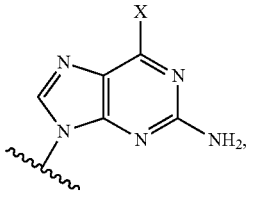


each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is



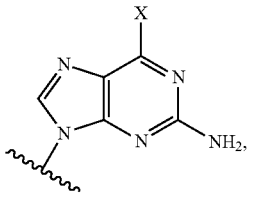
wherein B is as defined in the context of Formula VIII. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is —$(CR_2)_n$ B, wherein R and B are as defined in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



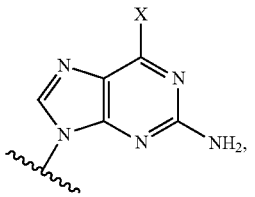
each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is —$(CR_2)_mNRC(O)D$; wherein R and D are as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is —$(CR_2)_mNRC(O)CH(OH)(CR_2)_2OH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is methoxyl; and each Z is —$(CR_2)_n$ $CR(R^A)C(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



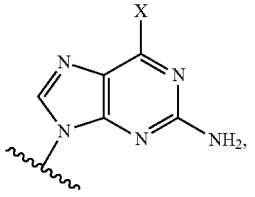
each Y is independently fluoro, acetoxyl, or hydroxyl and X is ethoxyl. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is ethoxyl; and each Z is —$(CR_2)_mC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



each Y is independently fluoro, acetoxyl, or hydroxyl; X is ethoxyl; and each Z is —$(CR_2)_mArC(O)O(CR_2)_nCR_3$; wherein R and Ar are as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is ethoxyl; and each Z is —$CR(E)(CR_2)_nOC(O)O(CR_2)_n$ CR_3; wherein R and E are as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

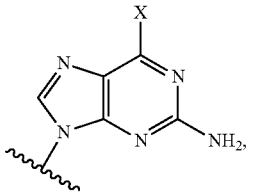
In certain embodiments, Base is



each Y is independently fluoro, acetoxyl, or hydroxyl; X is ethoxyl; and each Z is —$(CR_2)_mSC(O)(CR_2)_mOH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro,

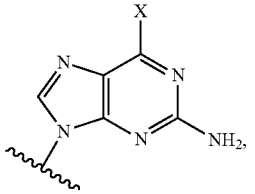
acetoxyl, or hydroxyl; X is ethoxyl; and each Z is —$(CR_2)_m$ $SC(O)(CR_2)_mOC(O)(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



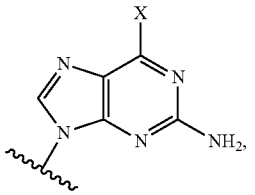
each Y is independently fluoro, acetoxyl, or hydroxyl; X is ethoxyl; and each Z is —(CR_2), $S—S(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

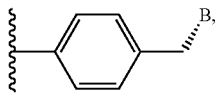


each Y is independently fluoro, acetoxyl, or hydroxyl; X is ethoxyl; and each Z is —$(CR_2)_mS—S(CR_2)_mOH$ wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is ethoxyl; and each Z is —$(CR_2)_n$ $NRC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

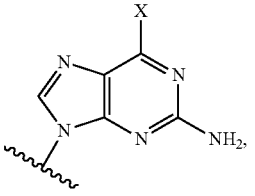


each Y is independently fluoro, acetoxyl, or hydroxyl; X is ethoxyl; and each Z is



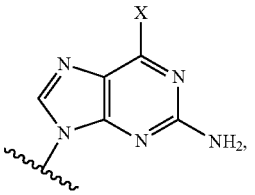
wherein B is as defined in the context of Formula VIII. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is ethoxyl; and each Z is —$(CR_2)_nB$, wherein R and B are as defined in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



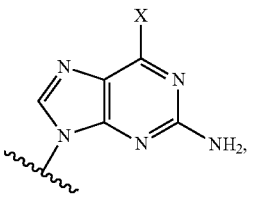
each Y is independently fluoro, acetoxyl, or hydroxyl; X is ethoxyl; and each Z is —$(CR_2)_mNRC(O)D$; wherein R and D are as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is ethoxyl; and each Z is —$(CR_2)_m$ $NRC(O)CH(OH)(CR_2)_2OH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, each Y is independently fluoro, acetoxyl, or hydroxyl; X is ethoxyl; and each Z is —$(CR_2)_nCR(R^A)C(O)$ $O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



Y is fluoro. In certain embodiments, Y is acetoxyl. In certain embodiments, Y is hydroxyl. In certain embodiments, Y is fluoro and each X is independently hydrogen, hydroxyl, methoxy or ethoxy. In certain embodiments, Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mC(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

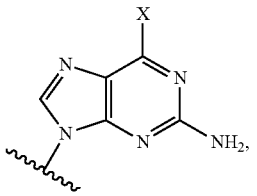
In certain embodiments, Base is



Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mArC(O)O$

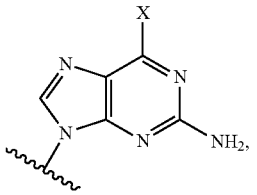
(CR_2)—CR_3; wherein R and Ar are as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10. In certain embodiments, Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$CR(E)(CR_2)_n$ $OC(O)O(CR_2)_nCR_3$; wherein R and E are as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



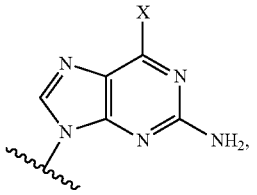
Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mSC(O)(CR_2)_m$ OH; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mSC(O)(CR_2)_mOC(O)(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



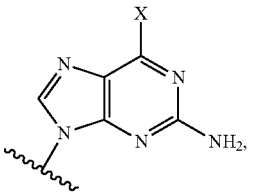
Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mS$—$S(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

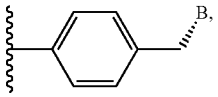


Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mS$—$S(CR_2)_mOH$ wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mNRC(O)O(CR_2)$—CR_3; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

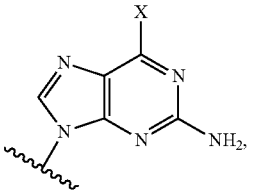


Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is



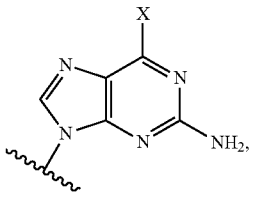
wherein B is as defined in the context of Formula VIII. In certain embodiments, Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_nB$, wherein R and B are as defined in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



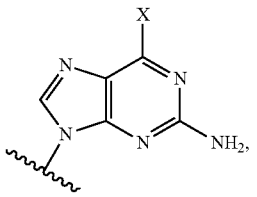
Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mNRC(O)D$; wherein R and D are as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mNRC(O)CH(OH)(CR_2)_2OH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is fluoro; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_nCR(R^4)C(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



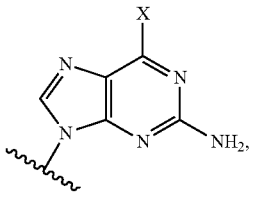
Y is acetoxyl and each X is independently hydrogen, hydroxyl, methoxy or ethoxy. In certain embodiments, Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is $—(CR_2)_mC(O)O(CR_2)—CR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



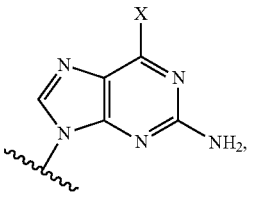
Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is $—(CR_2)_mArC(O)O(CR_2)—CR_3$; wherein R and Ar are as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10. In certain embodiments, Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is $—CR(E)(CR_2)_mOC(O)O(CR_2)—CR_3$; wherein R and E are as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



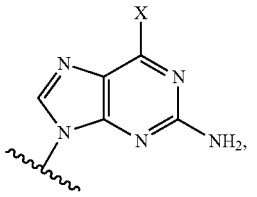
Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is $—(CR_2)_mSC(O)(CR_2)_mOH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is $—(CR_2)_mSC(O)(CR_2)_mOC(O)(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



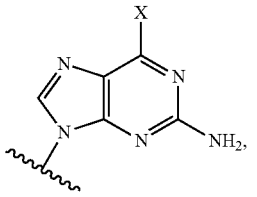
Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is $—(CR_2)_mS—S(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

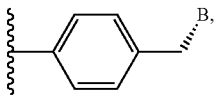


Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is $—(CR_2)_mS—S(CR_2)_mOH$ wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is $—(CR_2)_mNRC(O)O(CR_2)—CR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

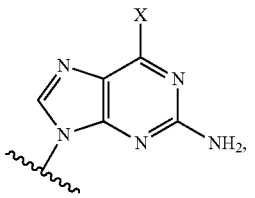


Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is



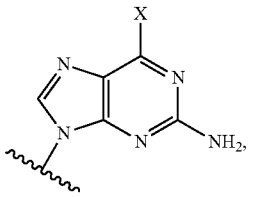
wherein B is as defined in the context of Formula VIII. In certain embodiments, Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is $—(CR_2)_1B$, wherein R and B are as defined in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



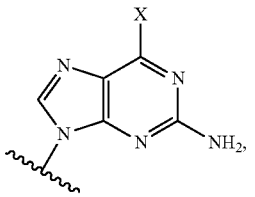
Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mNRC(O)D$; wherein R and D are as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mNRC(O)CH(OH)(CR_2)_2OH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is acetoxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_nCR(R^A)C(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



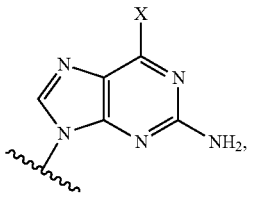
Y is hydroxyl and each X is independently hydrogen, hydroxyl, methoxy or ethoxy. In certain embodiments, Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mC(O)O(CR_2)$—CR_3; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



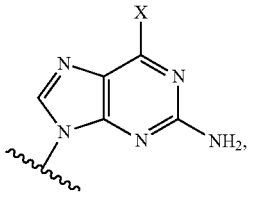
Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mArC(O)O(CR_2)$—CR_3; wherein R and Ar are as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10. In certain embodiments, Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$CR(E)(CR_2)_nOC(O)O(CR_2)$—$CR_3$; wherein R and E are as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



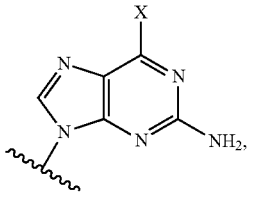
Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mSC(O)(CR_2)_mOH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mSC(O)(CR_2)_mOC(O)(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is



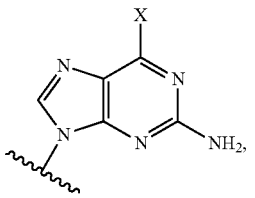
Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —(CR_2), S—$S(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

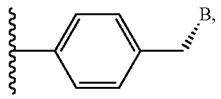


Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mS$—$S(CR_2)_mOH$ wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mNRC(O)O(CR_2)$—CR_3; wherein R is as defined herein in the context of Formula VIII; each m is independently an integer selected over the range of 1 to 10; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, Base is

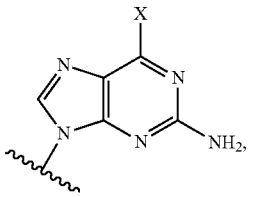


Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is



wherein B is as defined in the context of Formula VIII. In certain embodiments, Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_nB$, wherein R and B are as defined in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

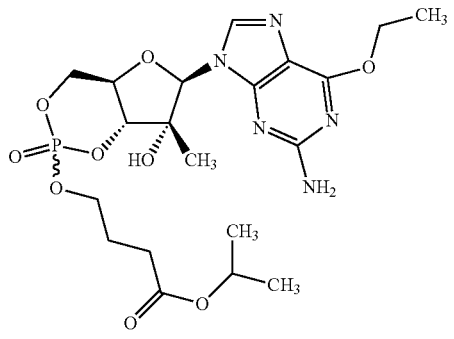
In certain embodiments, Base is



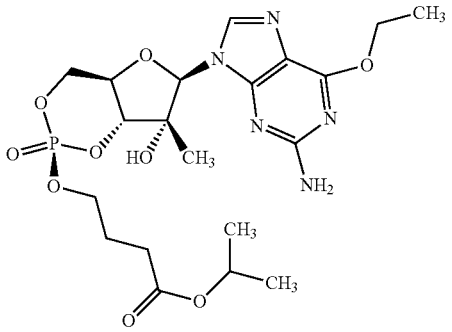
Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mNRC(O)D$; wherein R and D are as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_mNRC(O)CH(OH)(CR_2)_2OH$; wherein R is as defined herein in the context of Formula VIII; and each m is independently an integer selected over the range of 1 to 10. In certain embodiments, Y is hydroxyl; each X is independently hydrogen, hydroxyl, methoxy or ethoxy; and each Z is —$(CR_2)_nCR(R^A)C(O)O(CR_2)_nCR_3$; wherein R is as defined herein in the context of Formula VIII; and each n is independently an integer selected over the range of 0 to 10.

In certain embodiments, provided herein are compounds according to any of formulas I-67b:

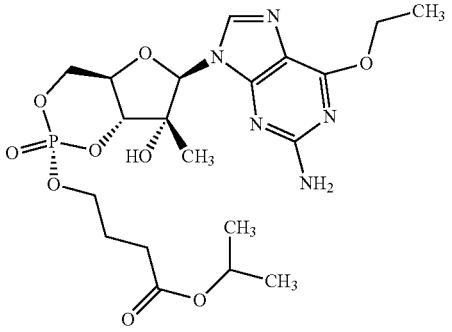
(1)



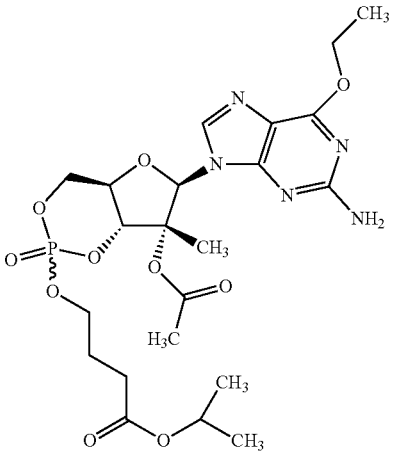
(1a)



(1b)



(2)



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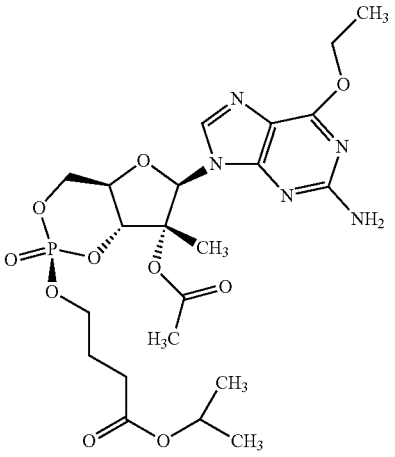
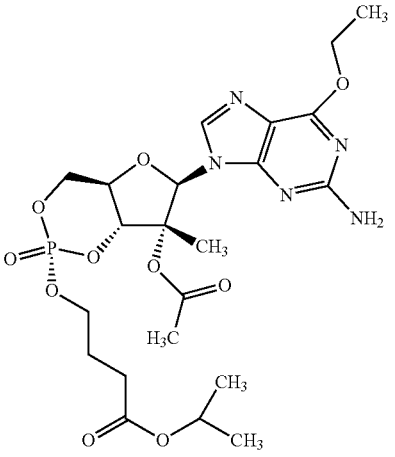
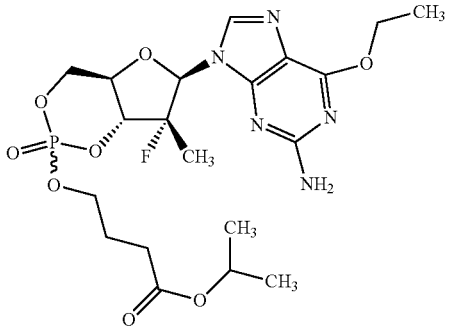
(2a)



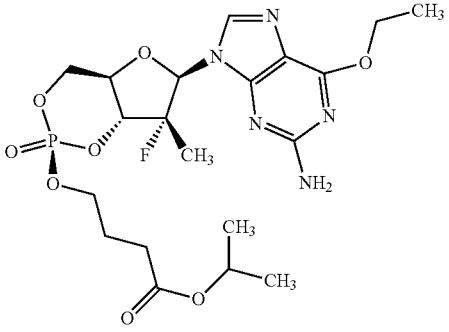
(2b)



(3)



(3a)



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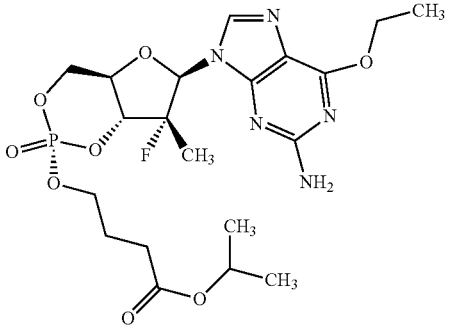
(3b)



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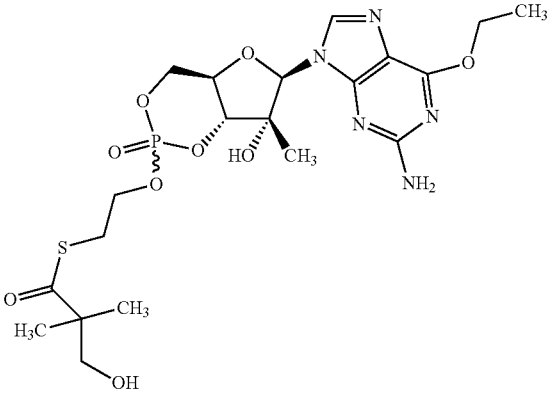
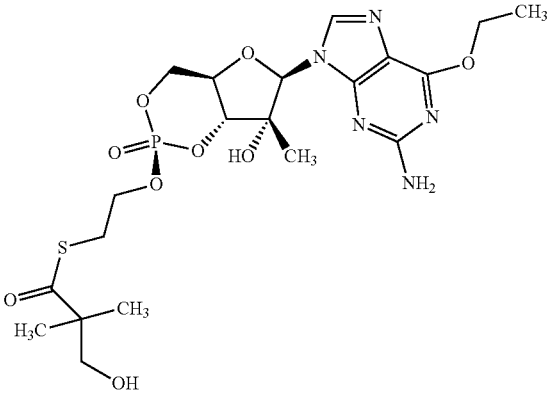
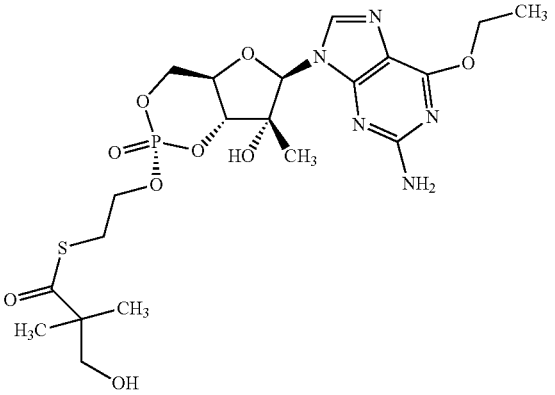


(4a)



(4b)



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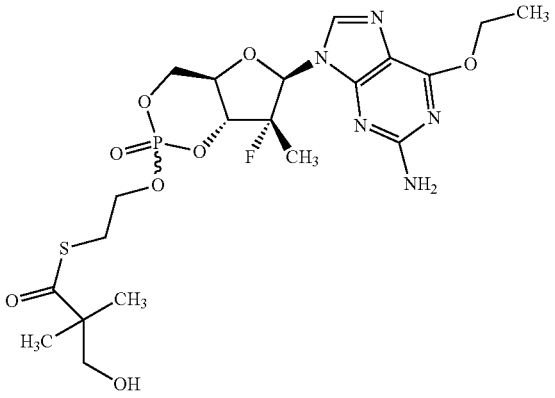
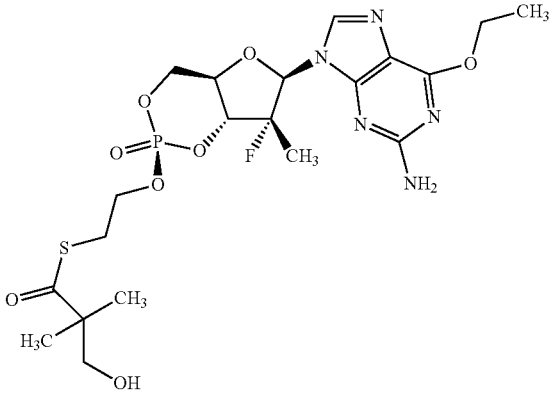
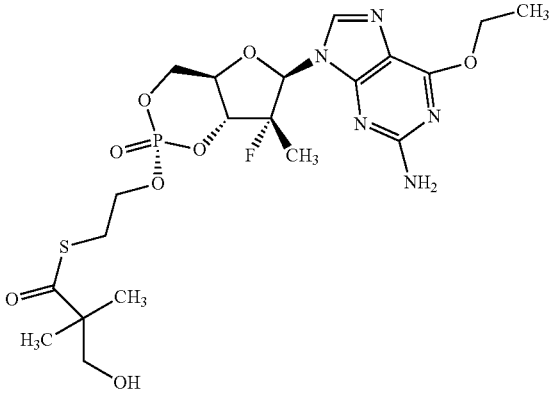


(5a)



(5b)



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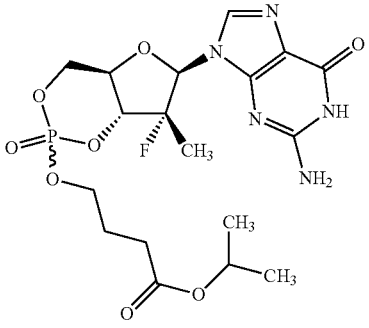

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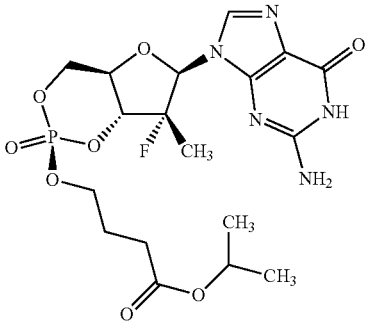
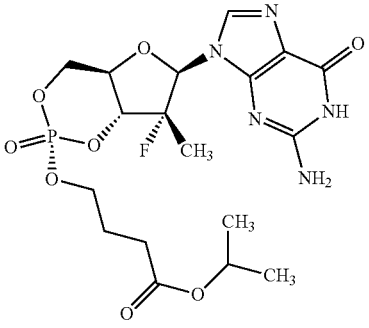
(6a)



(6b)



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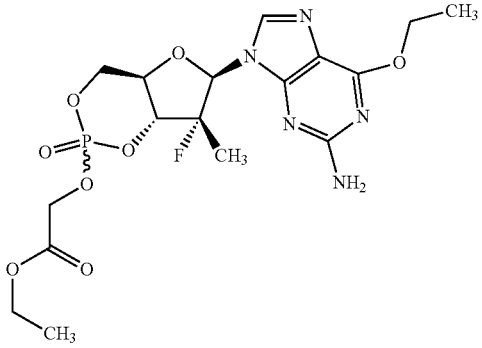
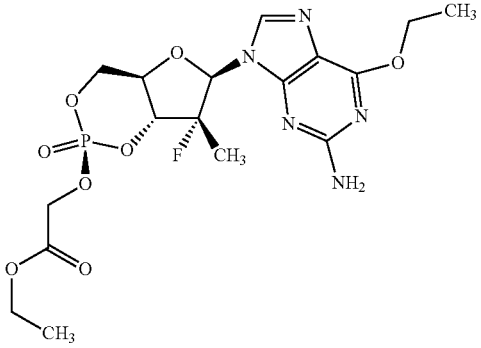


(7a)



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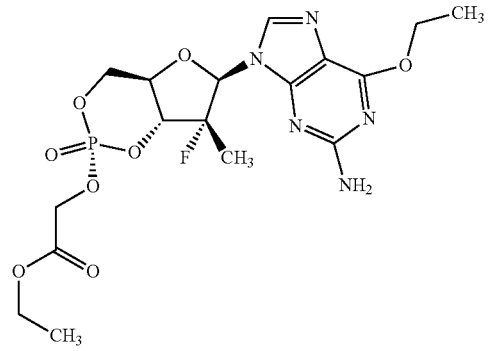
(7b)



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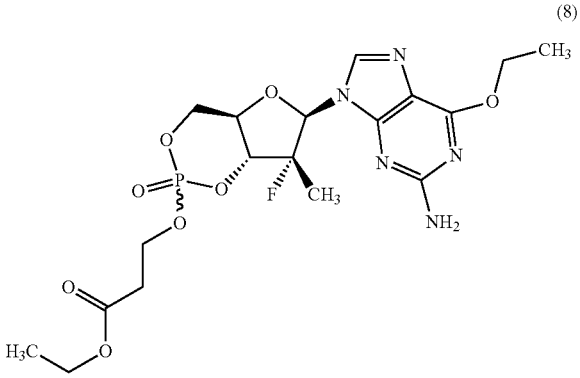
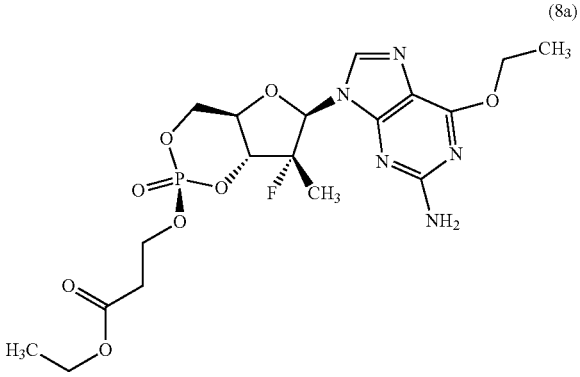


(8a)



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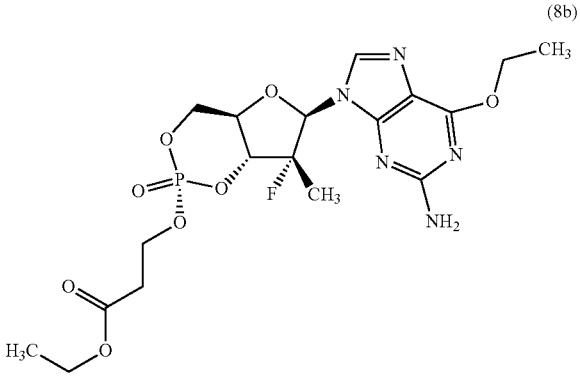

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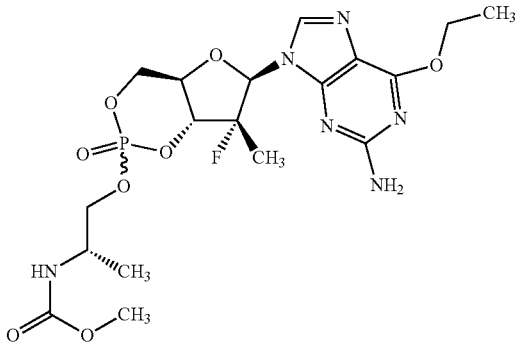

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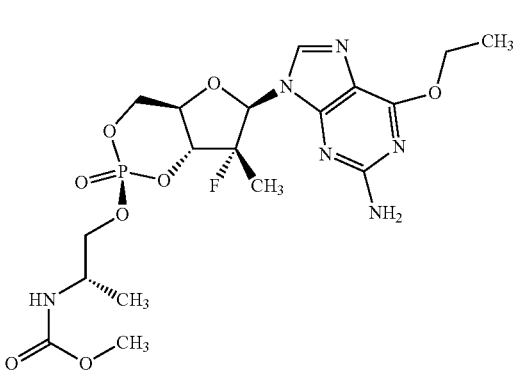
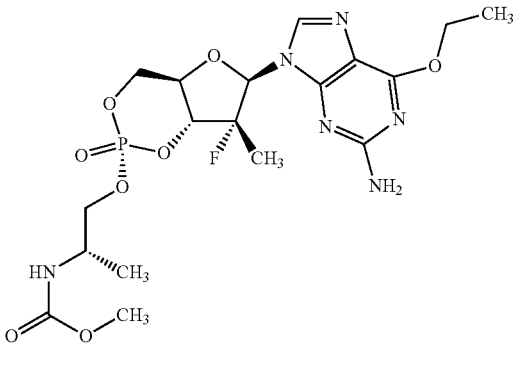


(9b)



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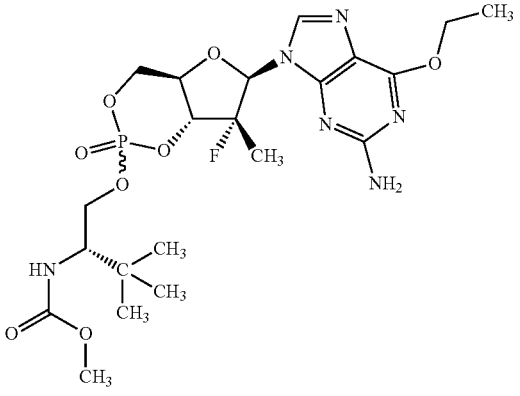

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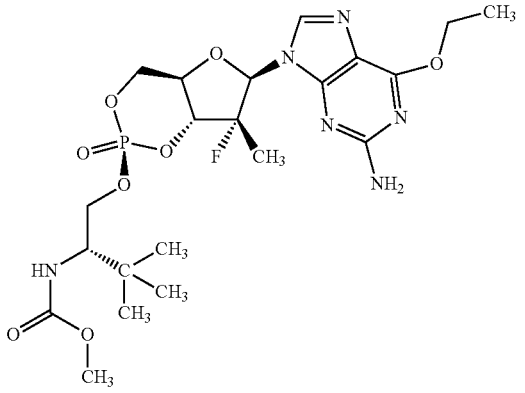
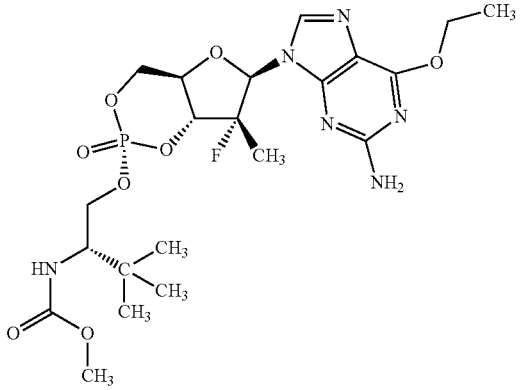


(10b)



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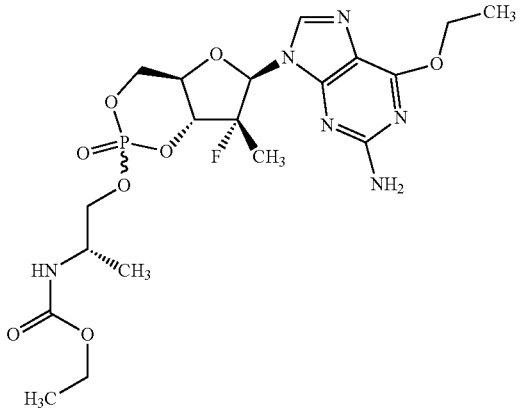

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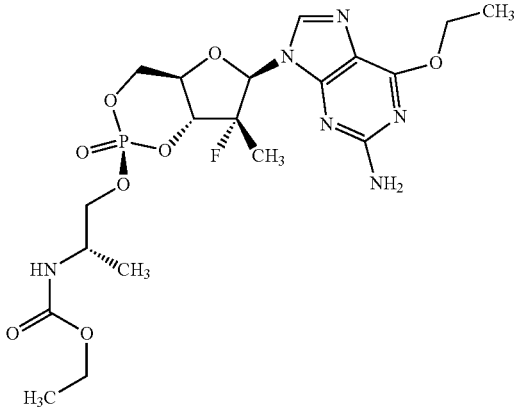
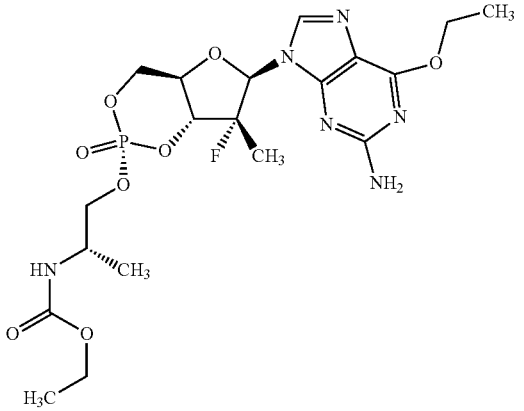
(11a)



(11b)



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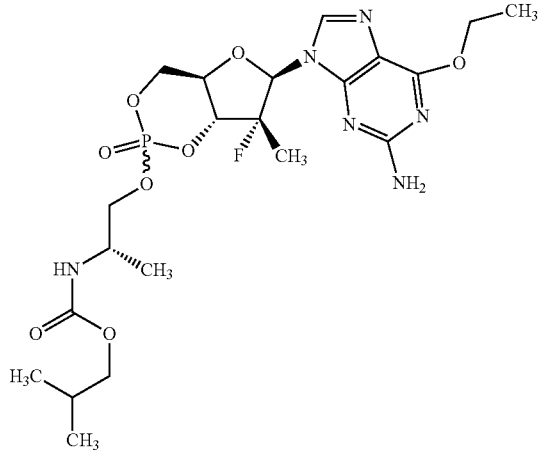

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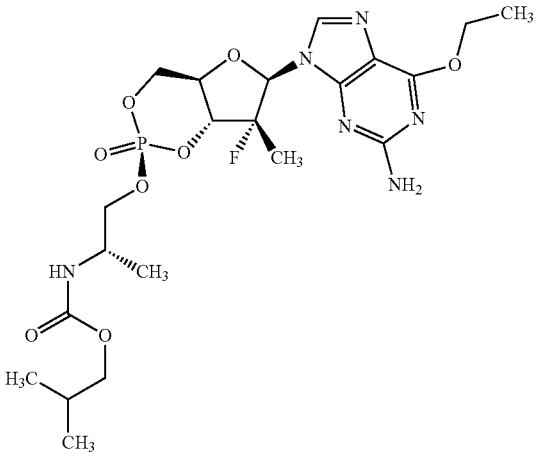
(12a)



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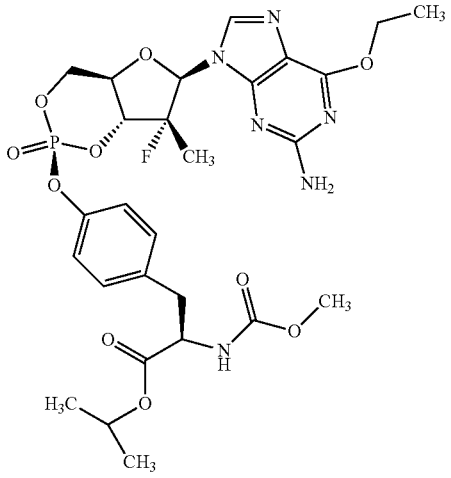

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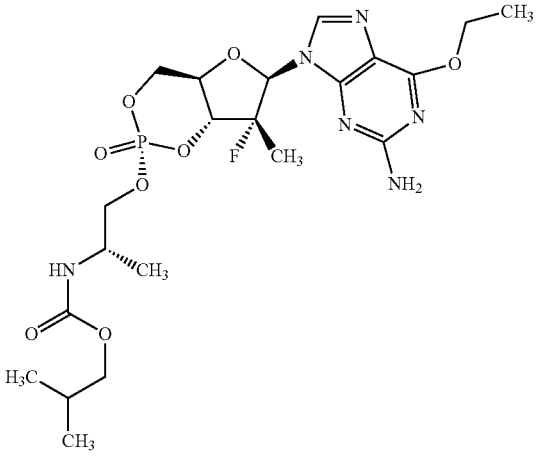

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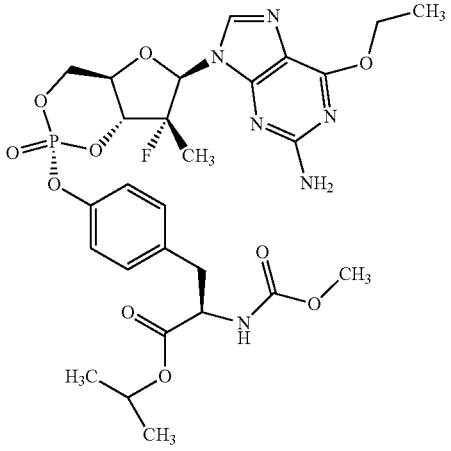

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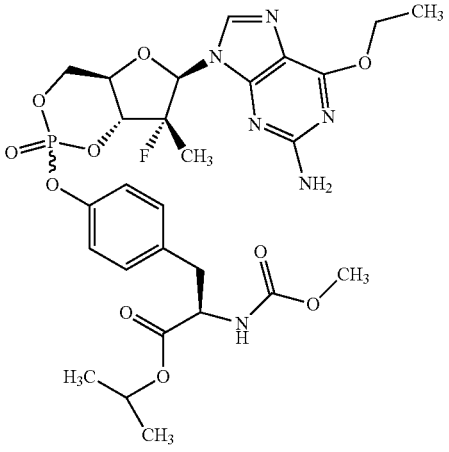

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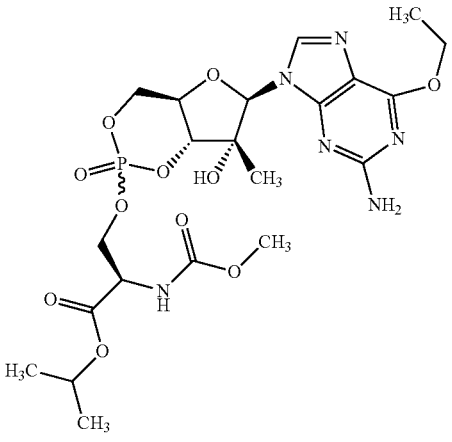

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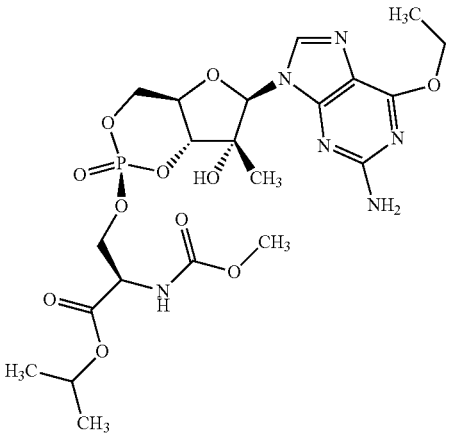

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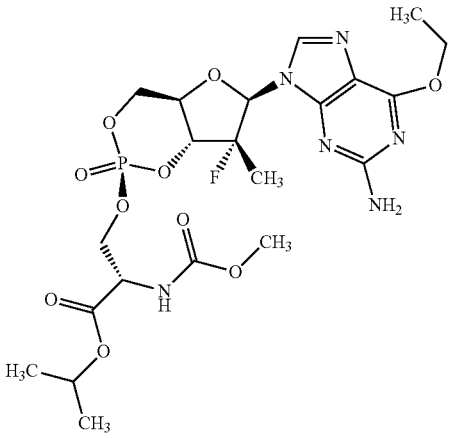

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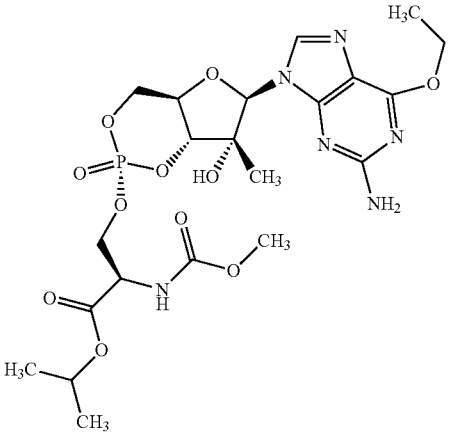

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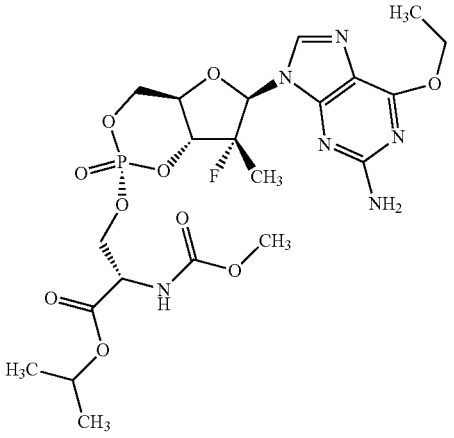

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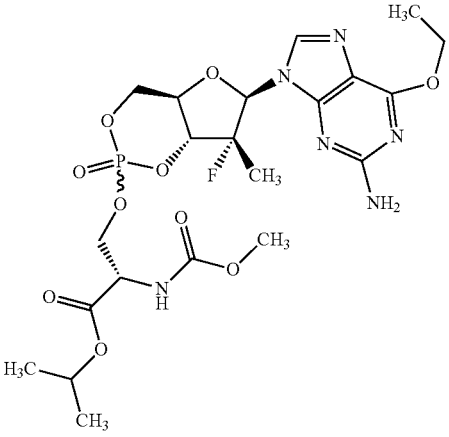

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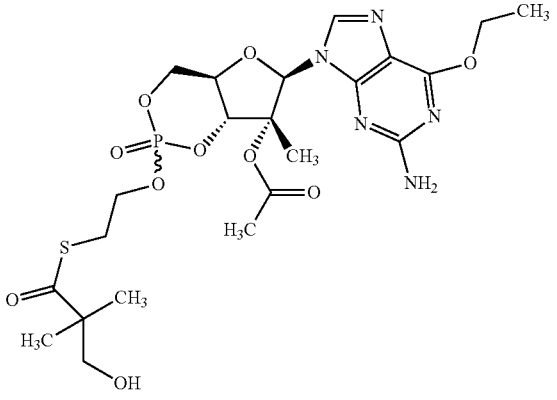

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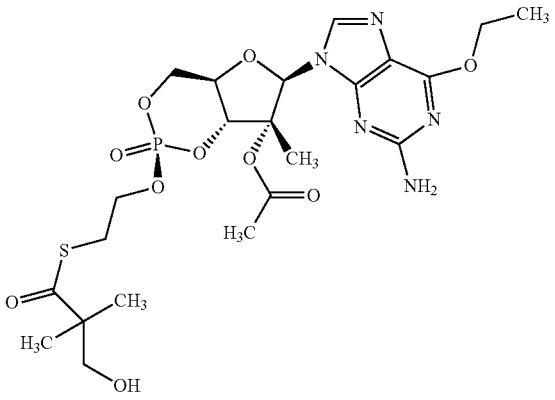

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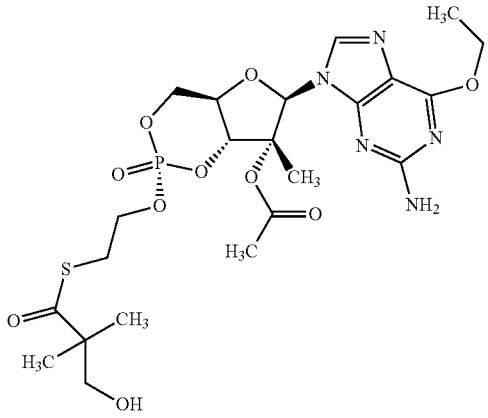

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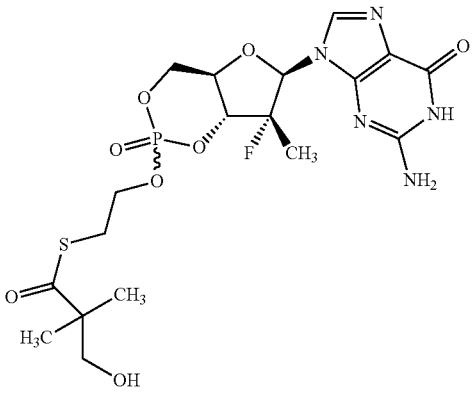
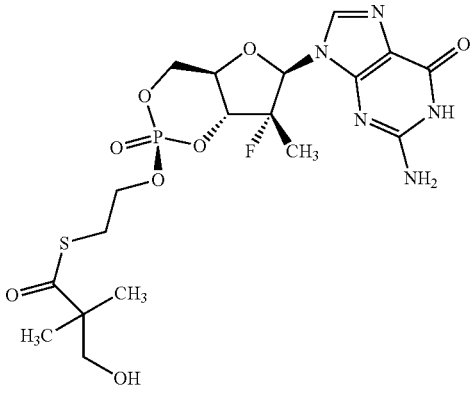


(17a)



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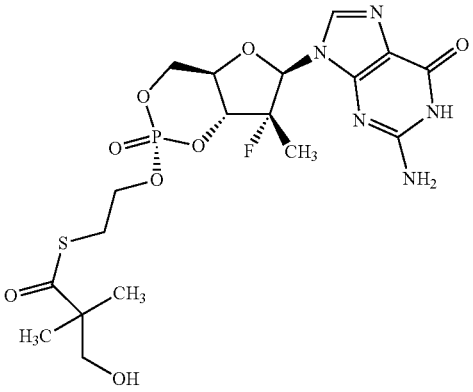
(17b)



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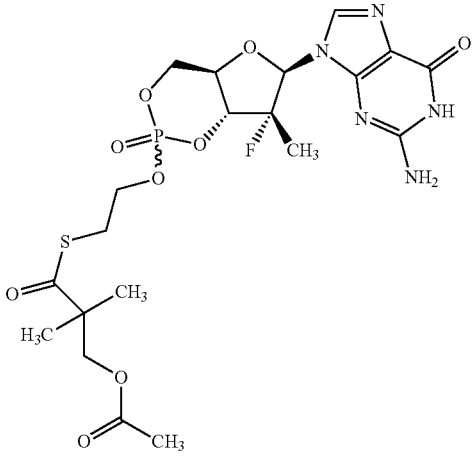

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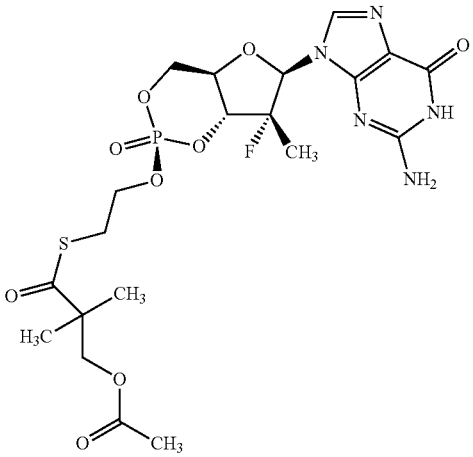

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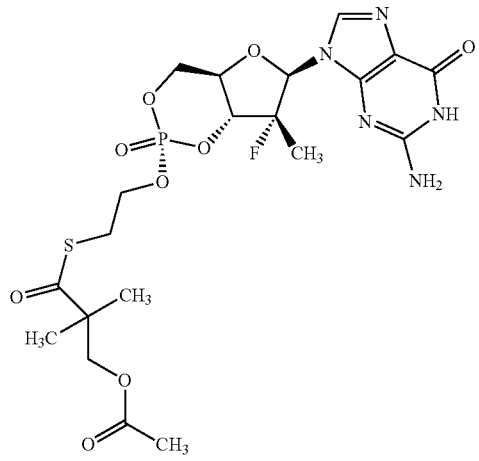

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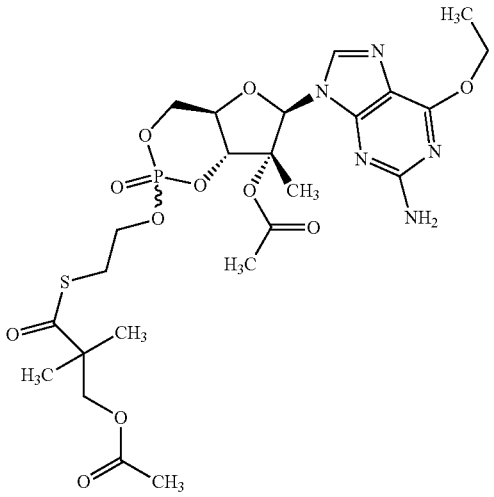

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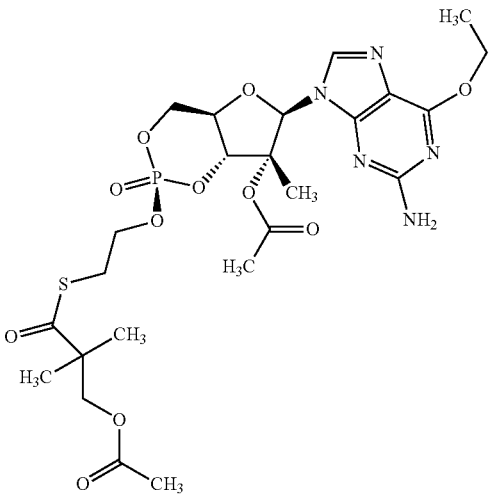

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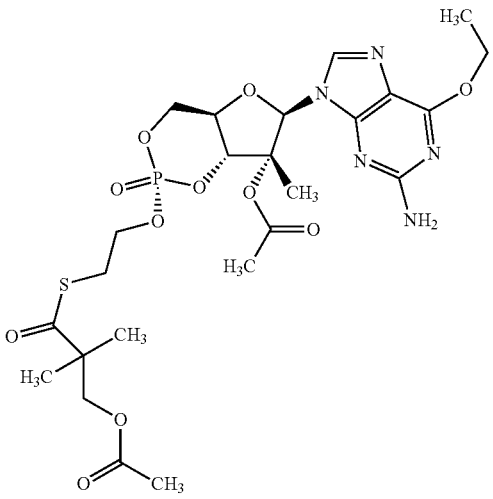

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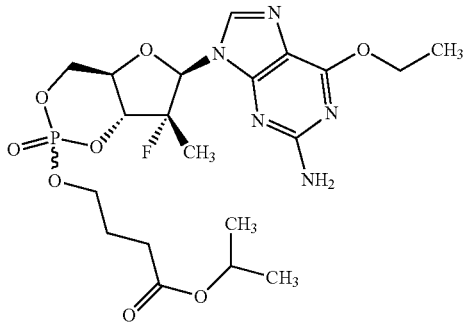

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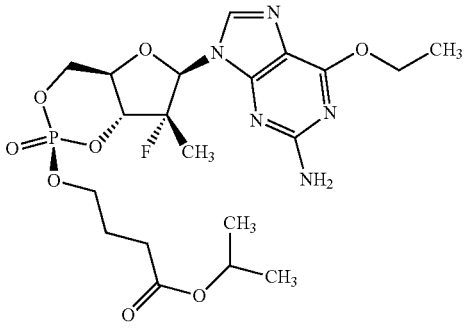

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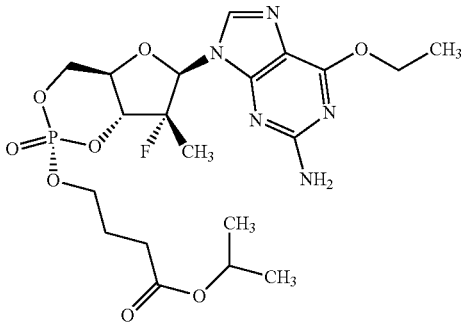

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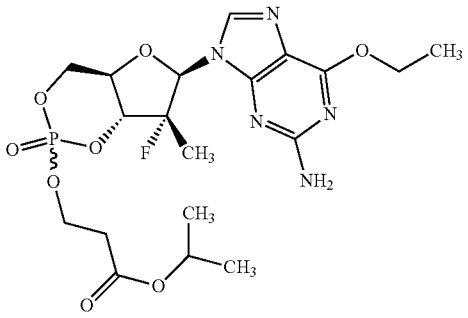

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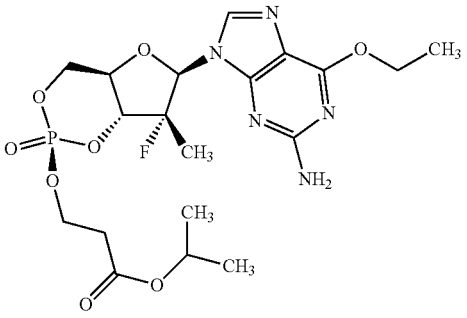

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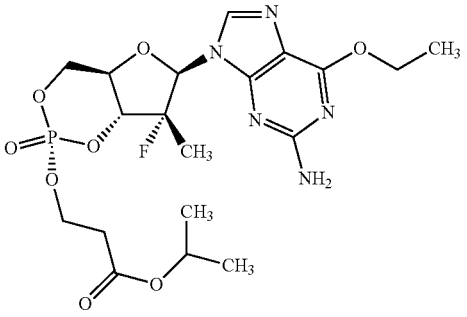

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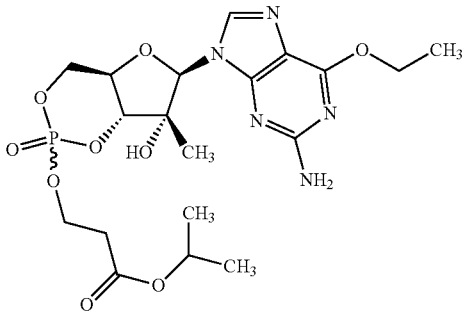

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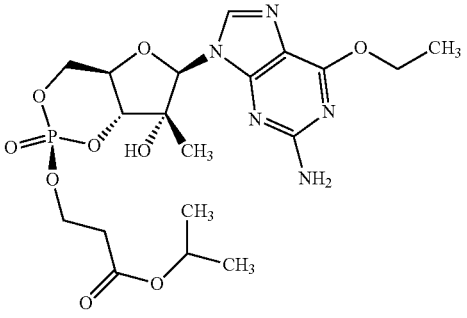

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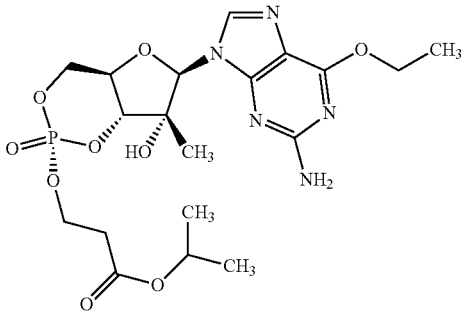

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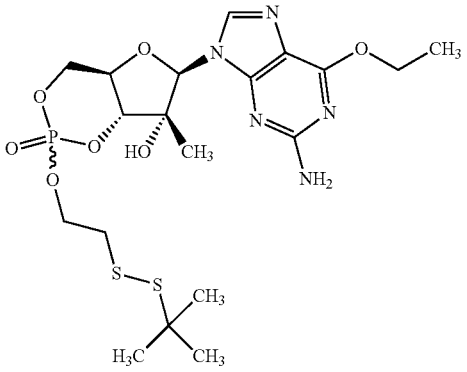

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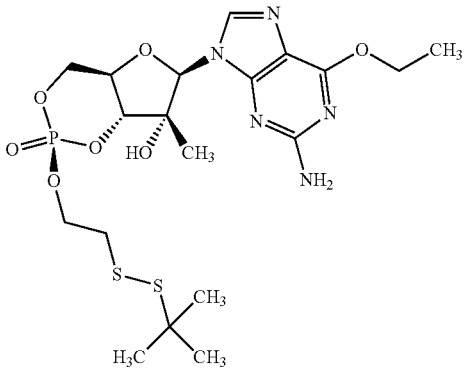

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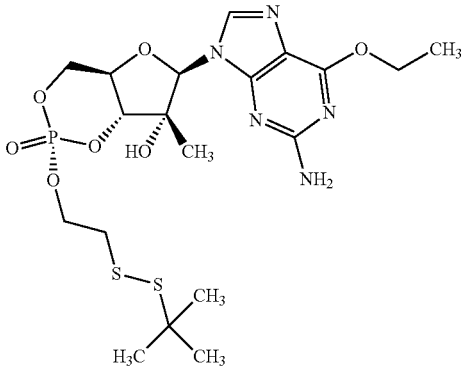

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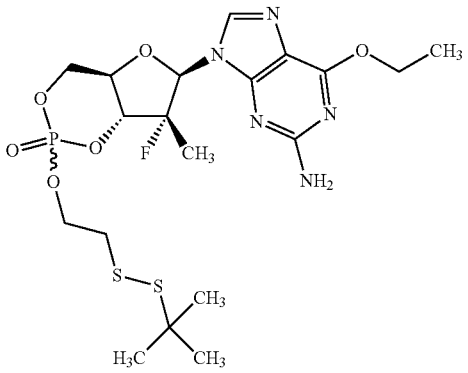

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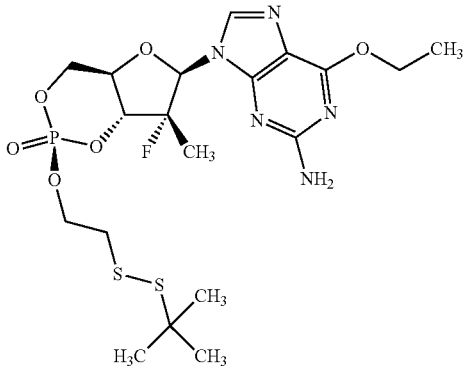

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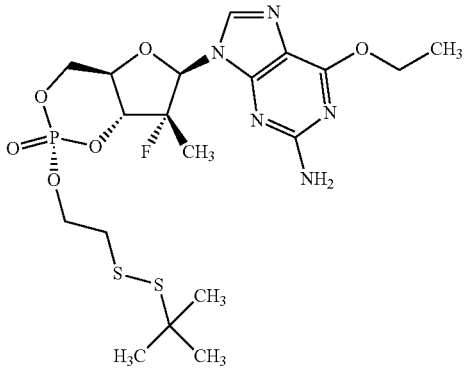

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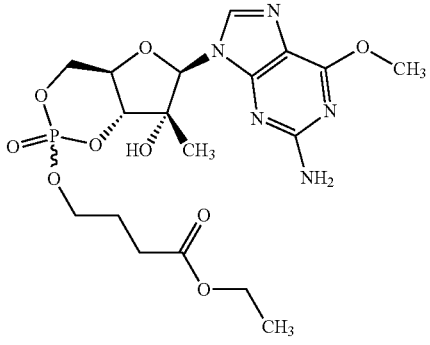

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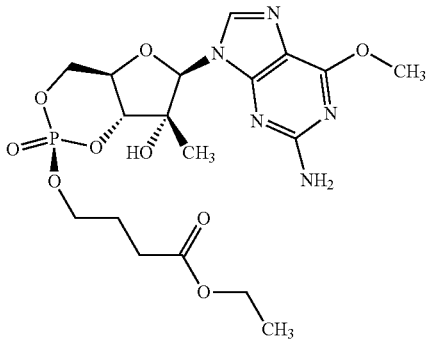

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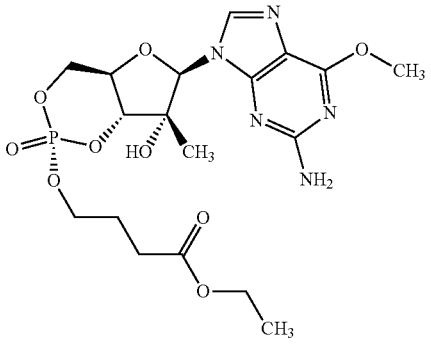

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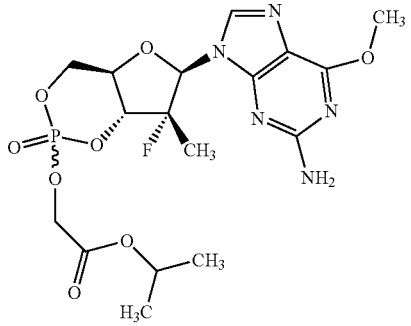

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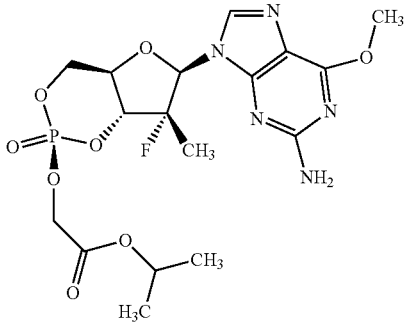

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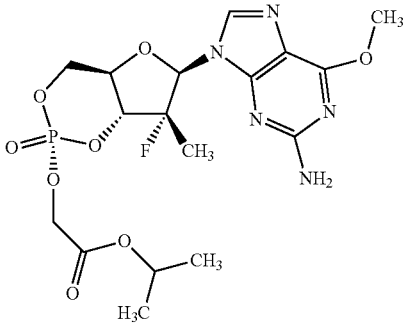

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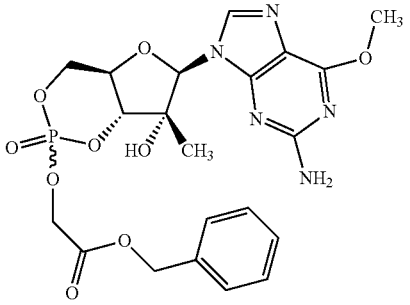

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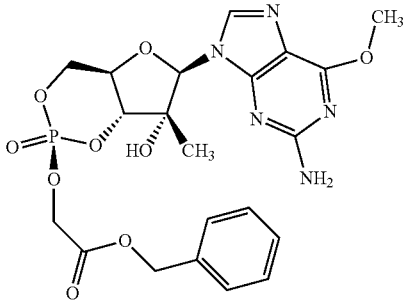

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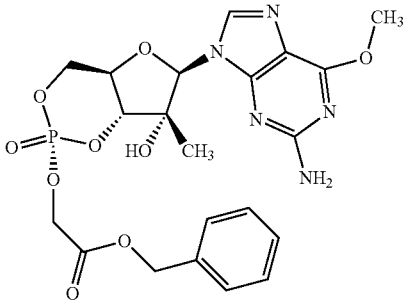

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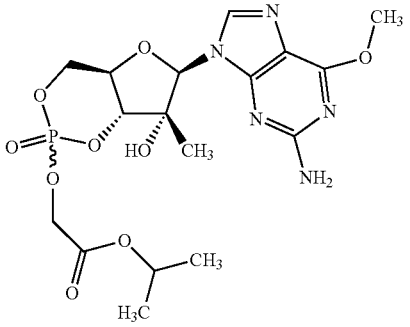

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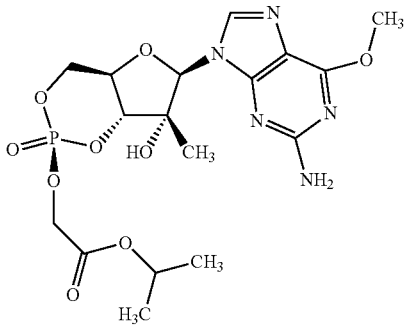

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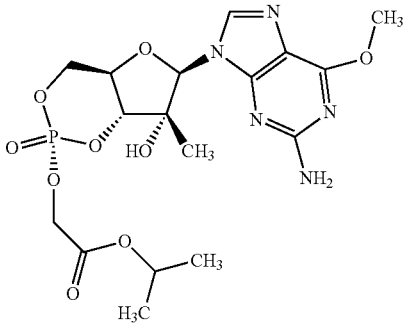

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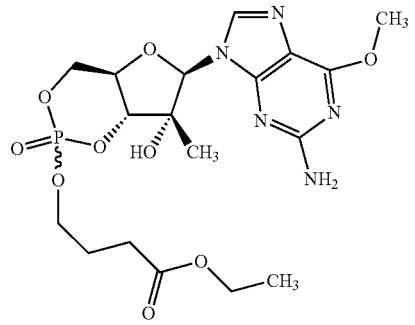

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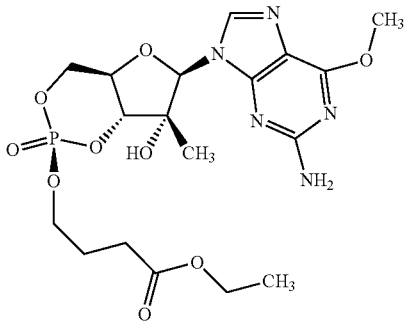

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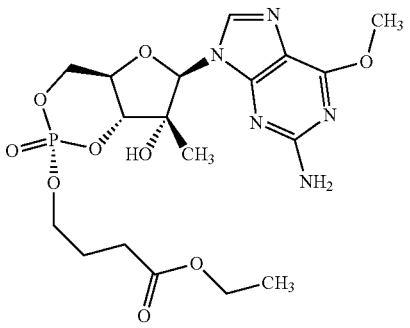

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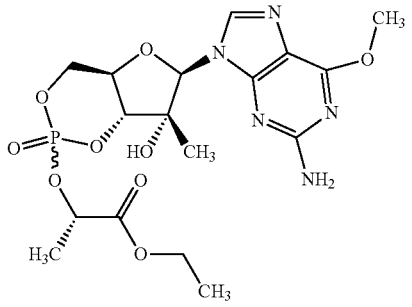

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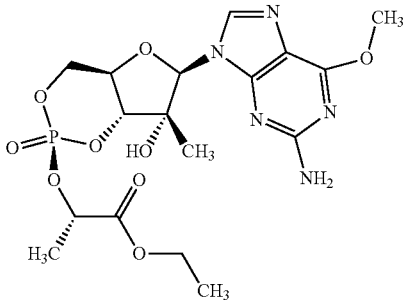

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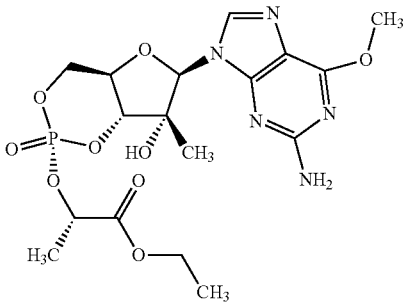

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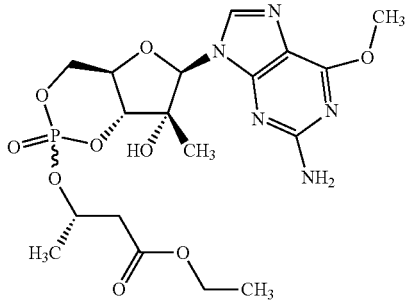

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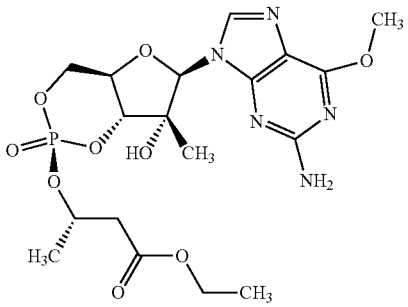

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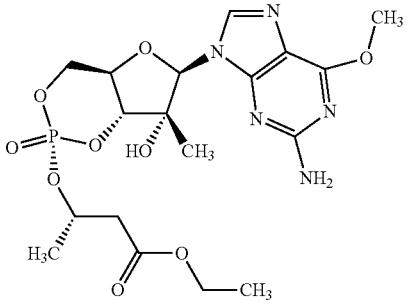

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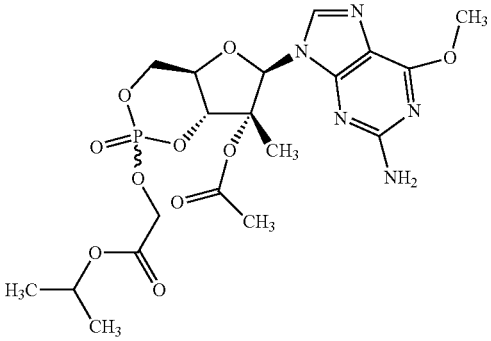

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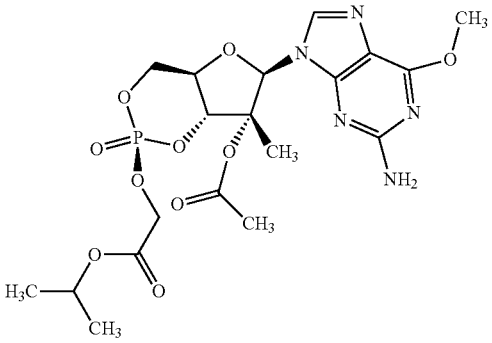

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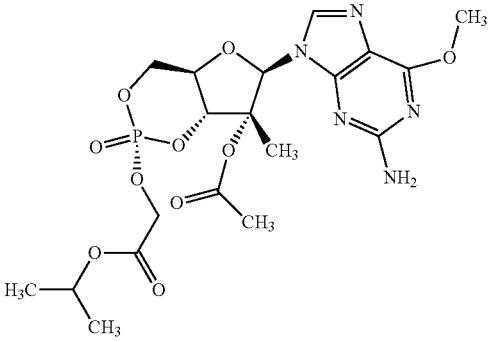

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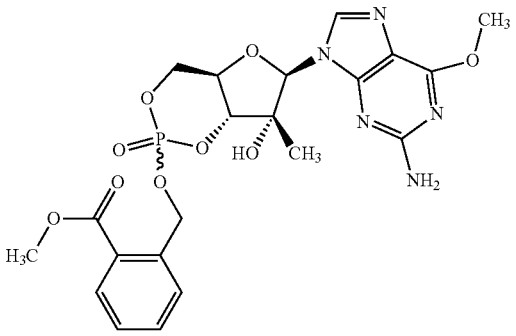

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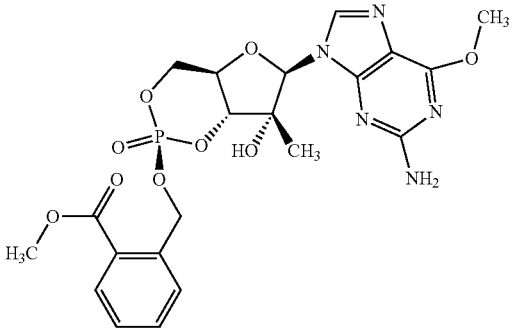

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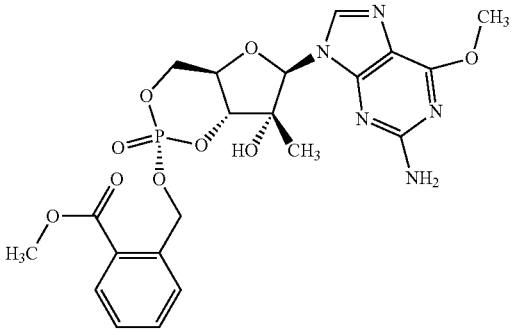

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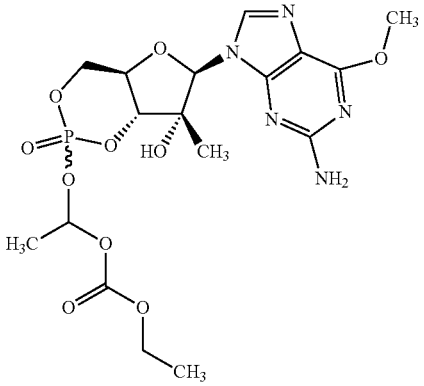

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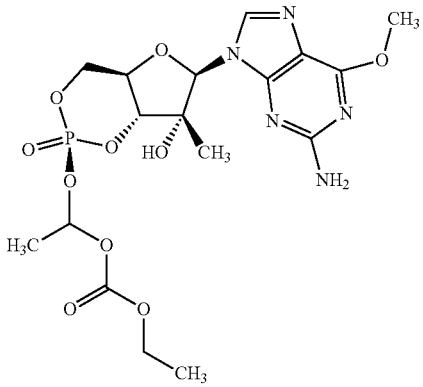

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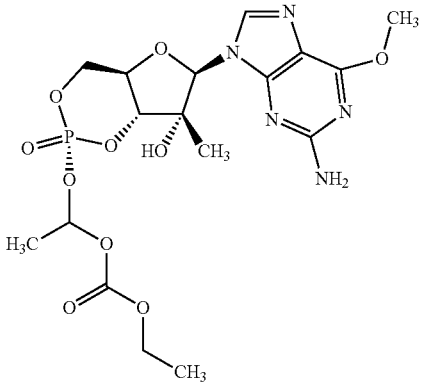

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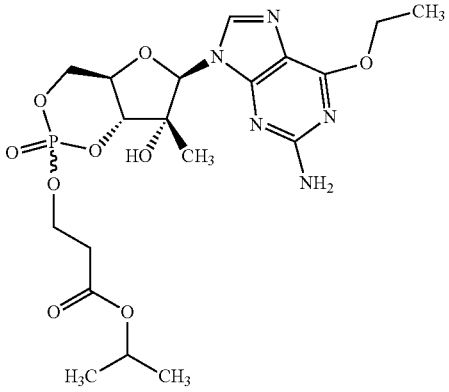

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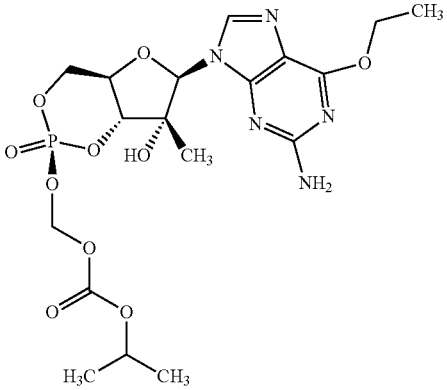

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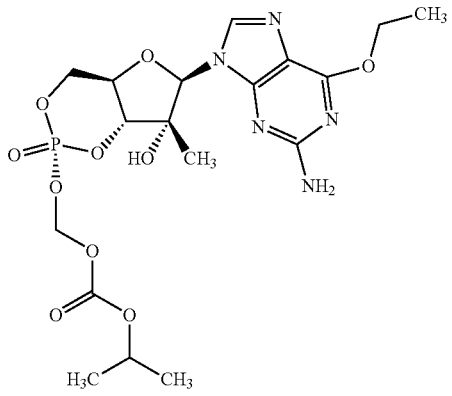

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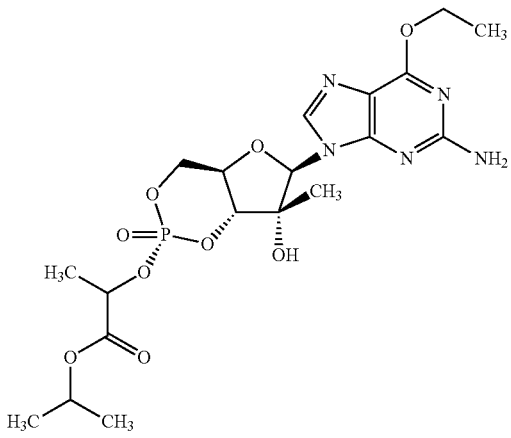

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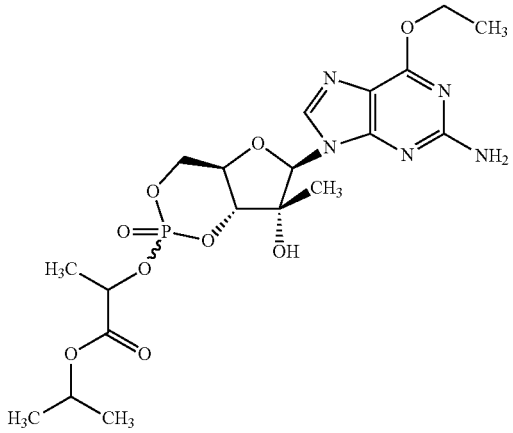

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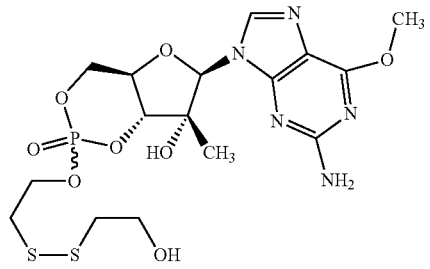

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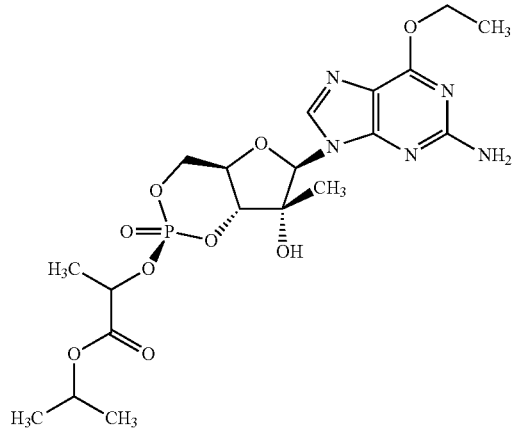

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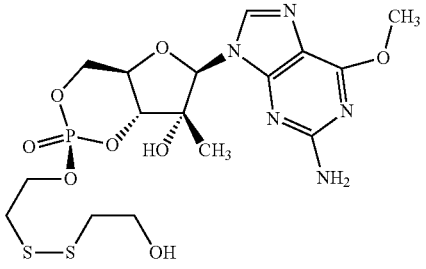

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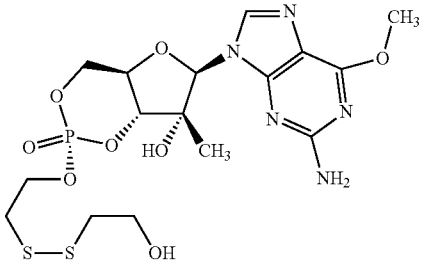

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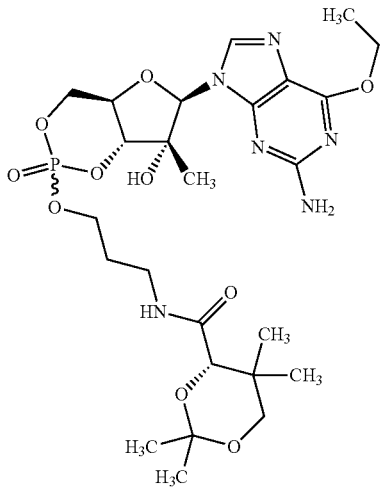
(38)



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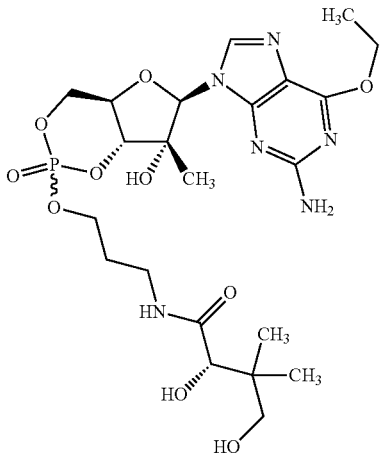

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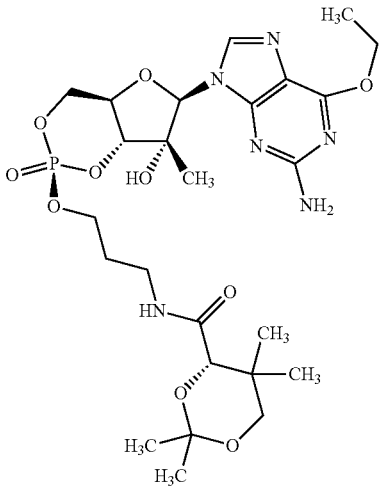

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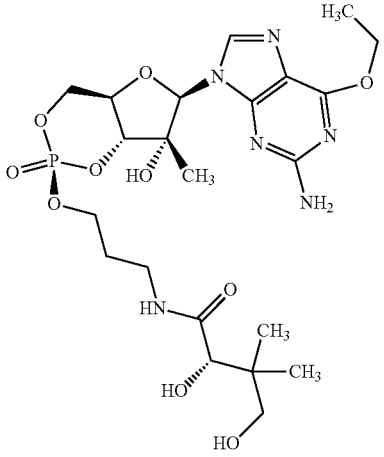

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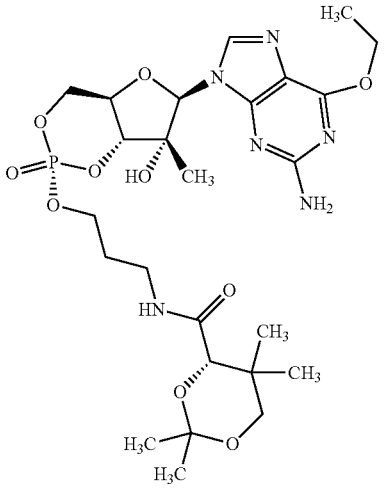

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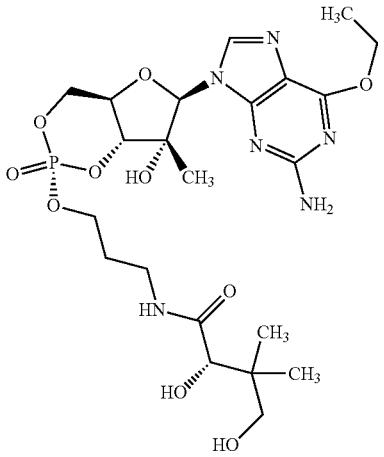

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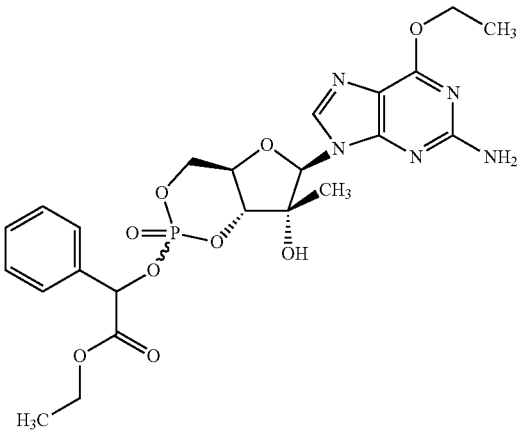

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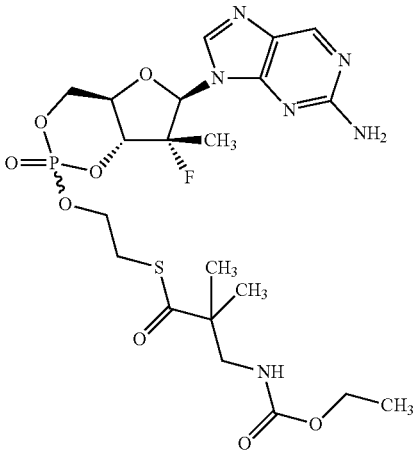

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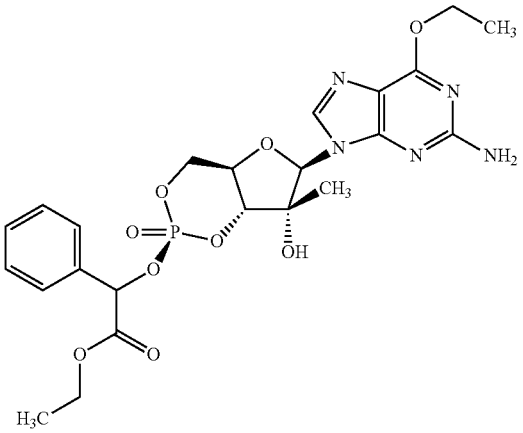

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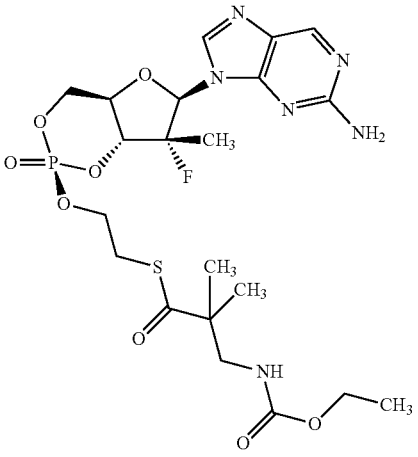

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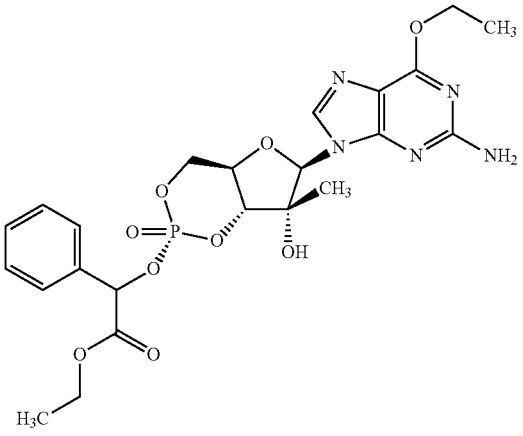

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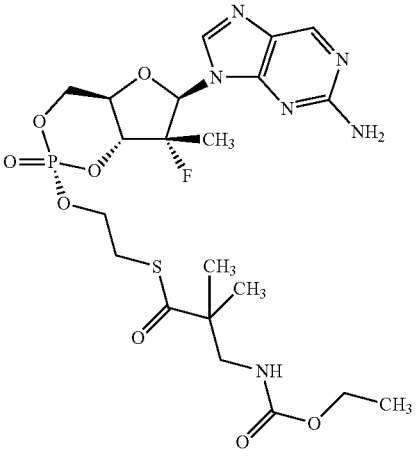

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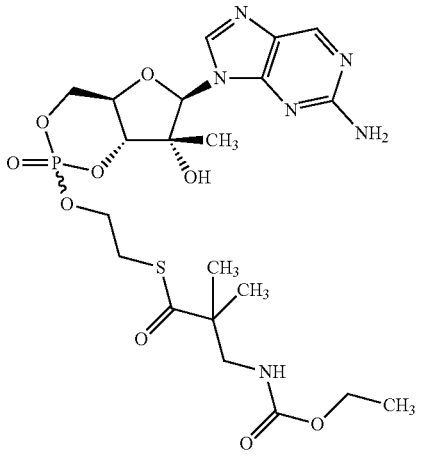

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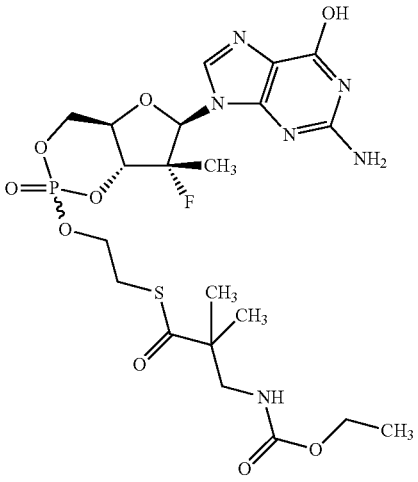

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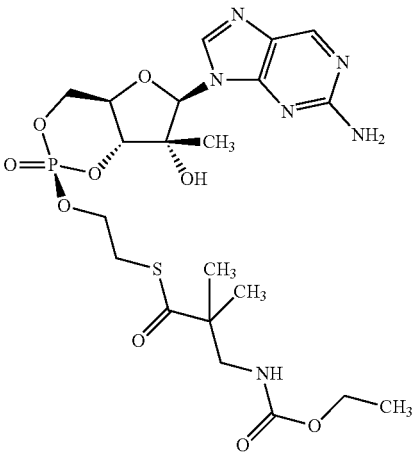

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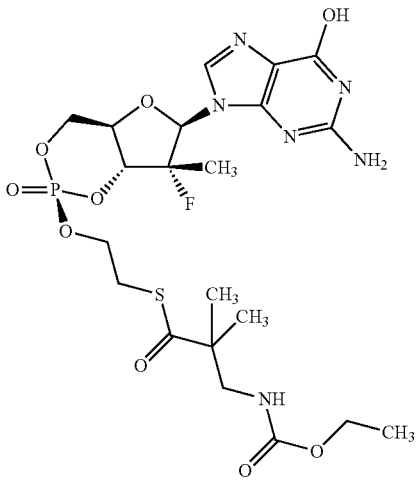

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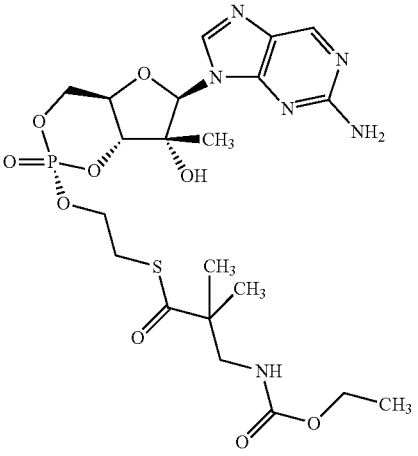

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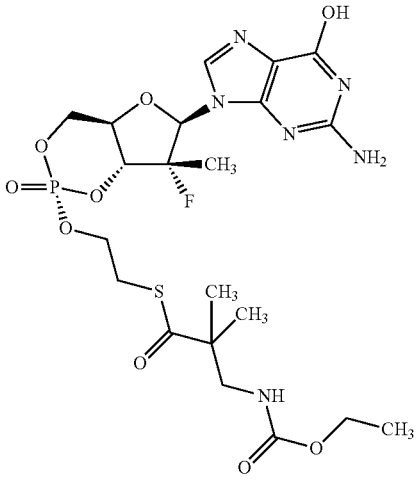

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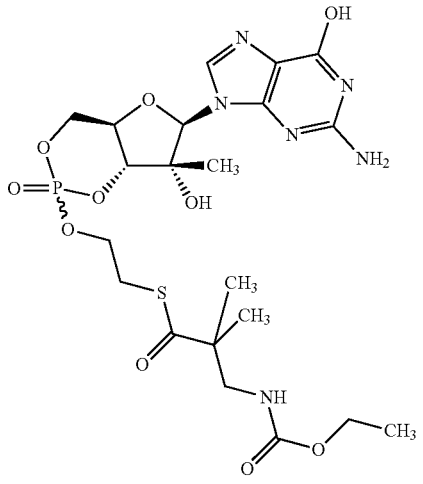

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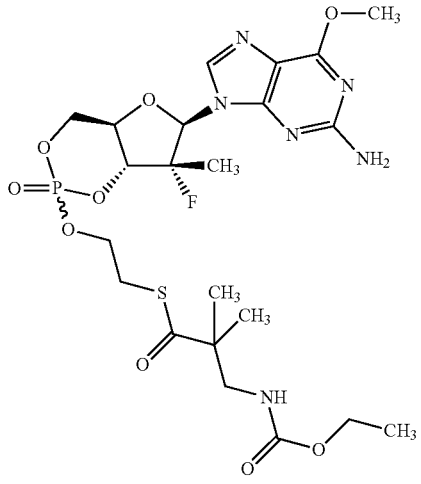

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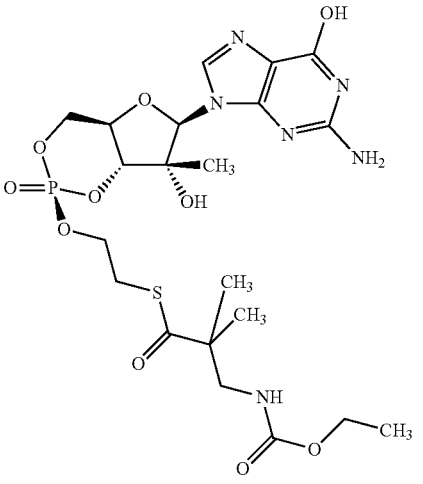

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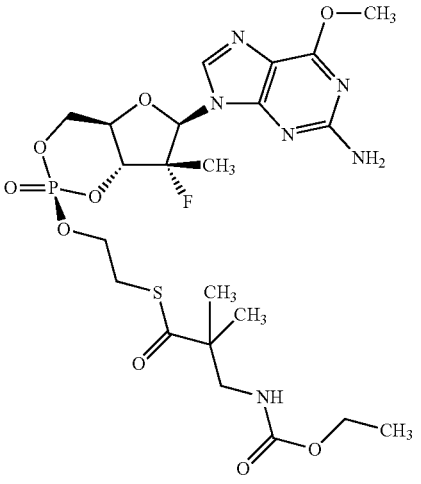

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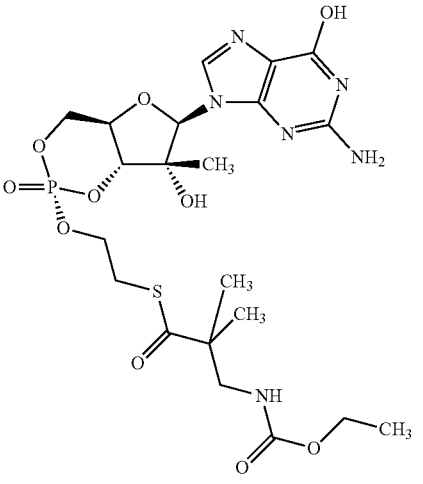

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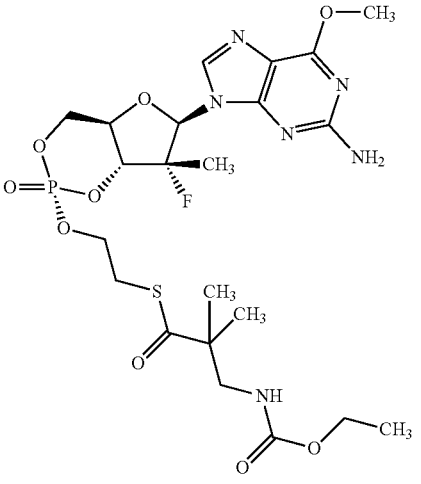

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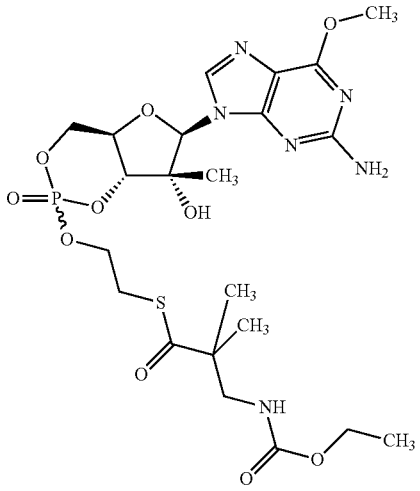

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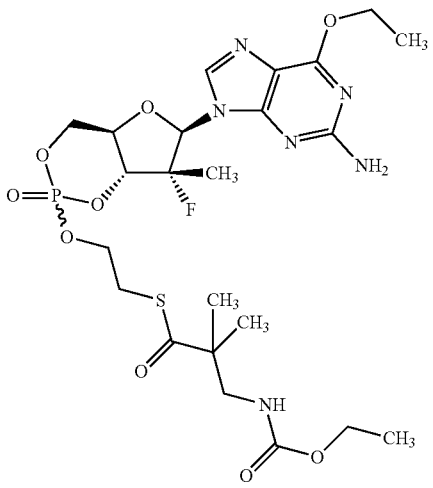

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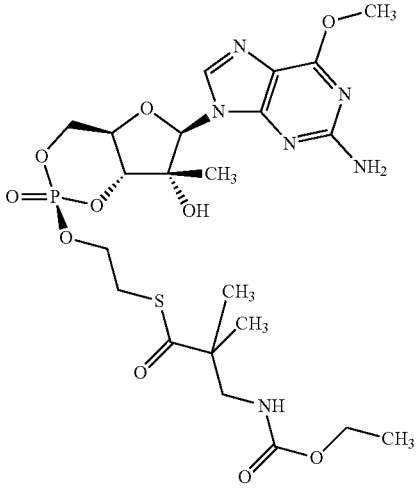

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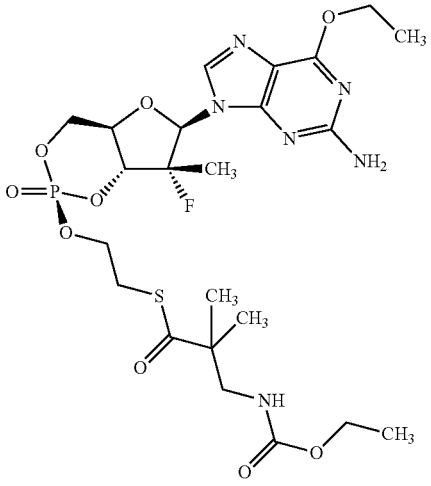

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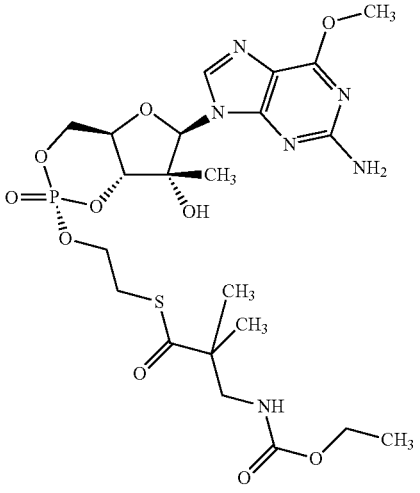

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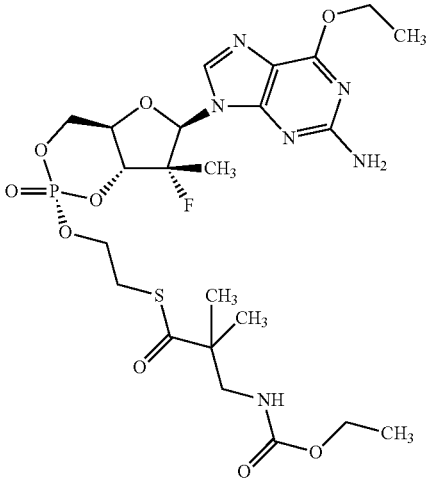

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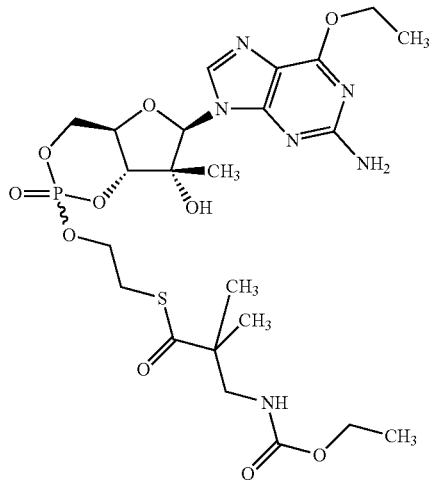

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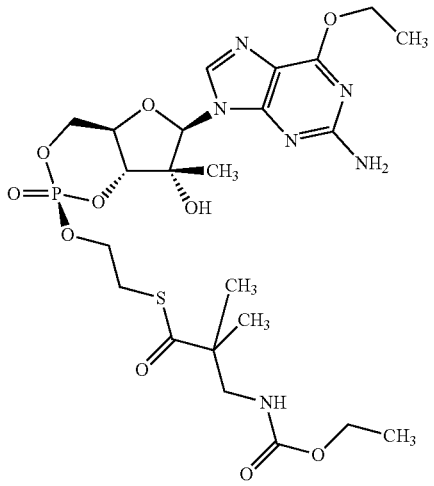

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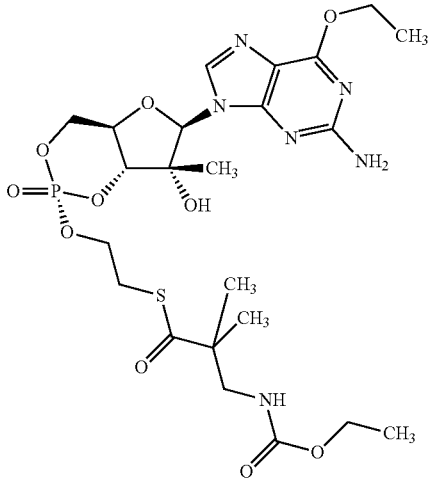

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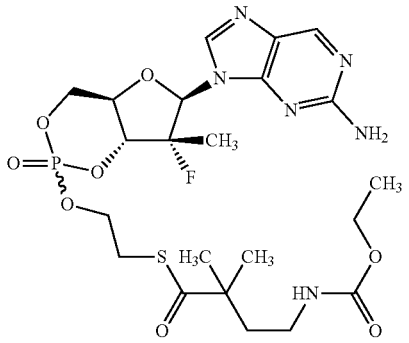

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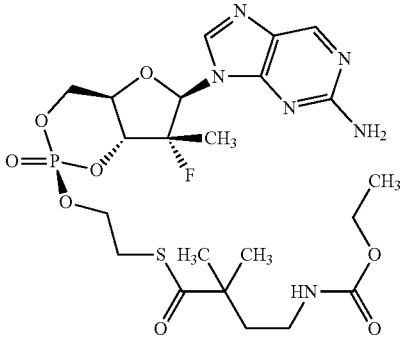

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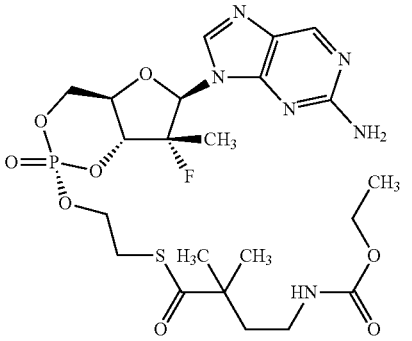

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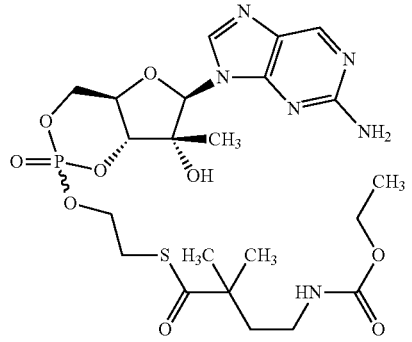

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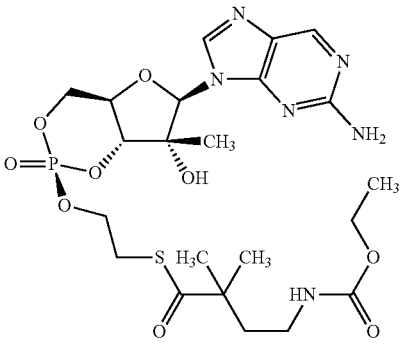

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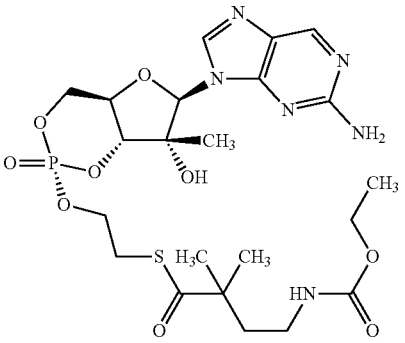

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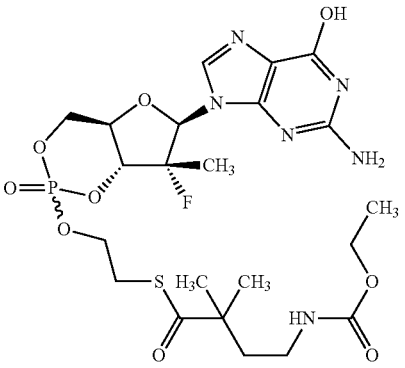

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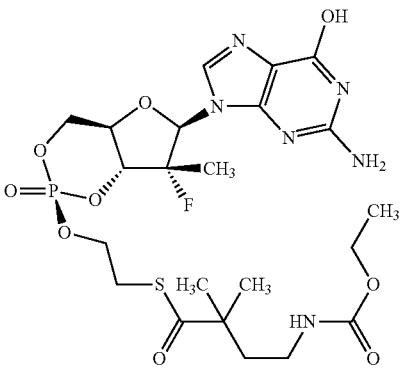

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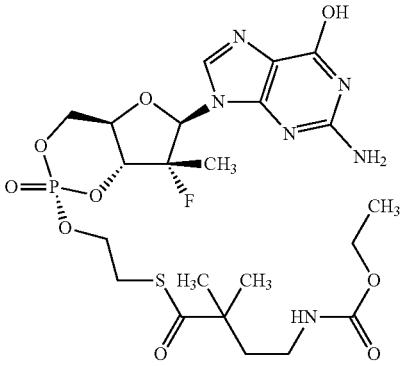

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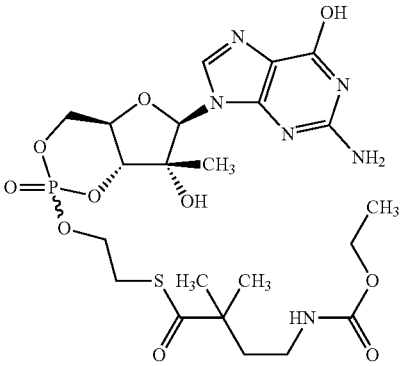

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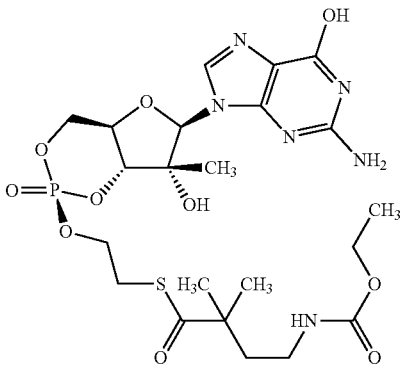

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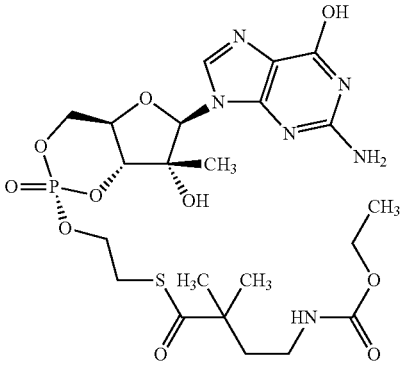

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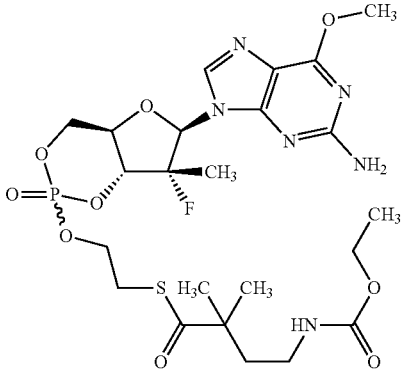

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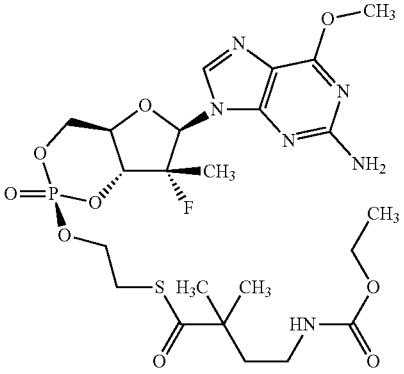

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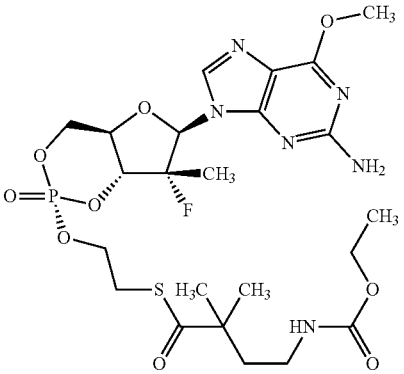

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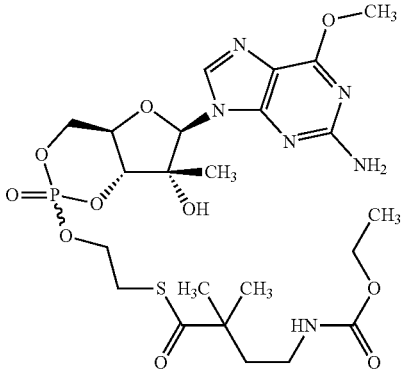

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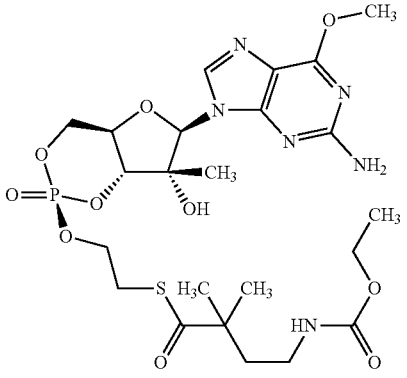

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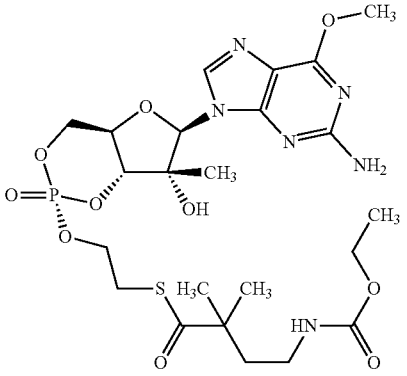

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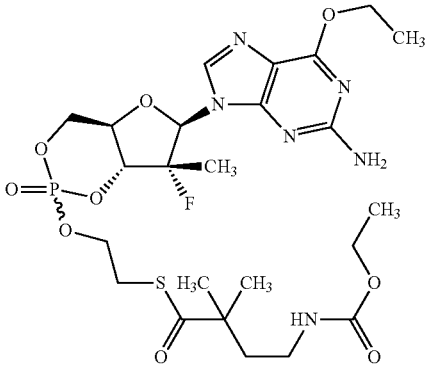

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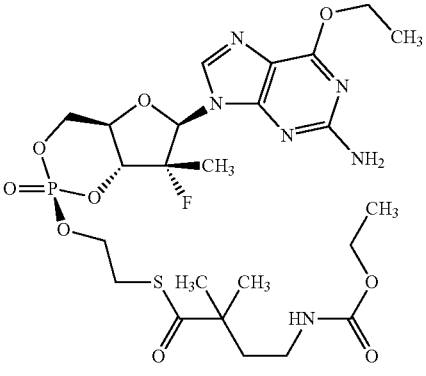

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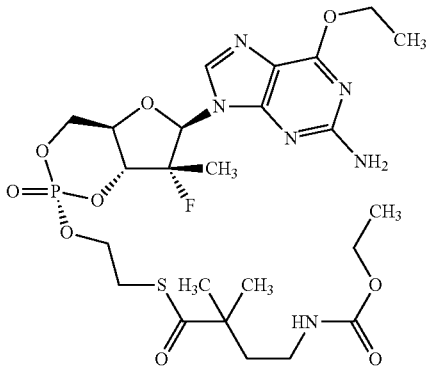

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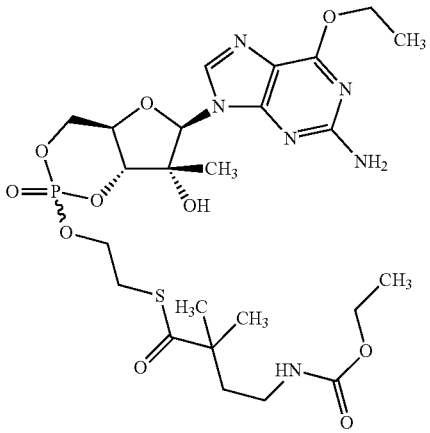

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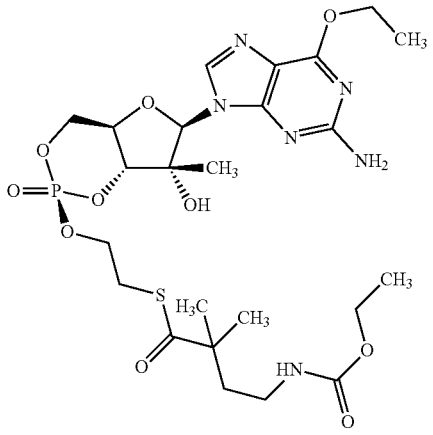

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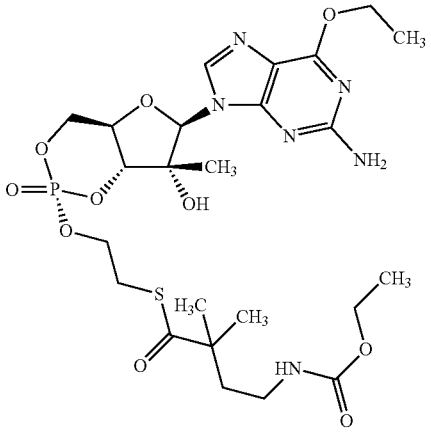

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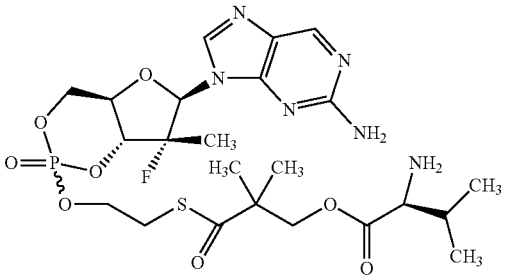

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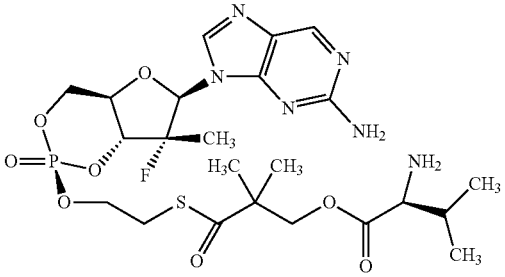

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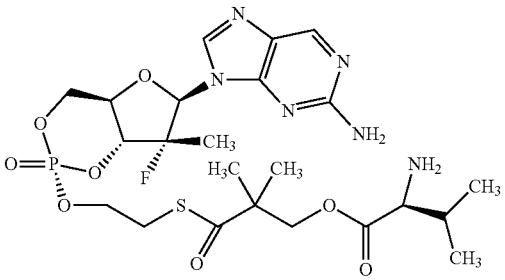

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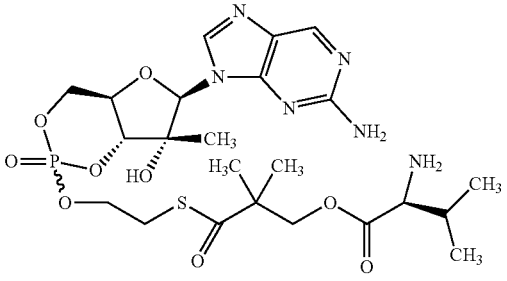

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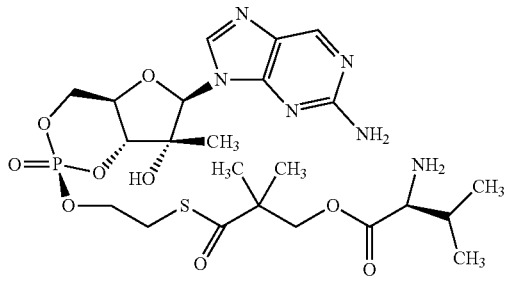

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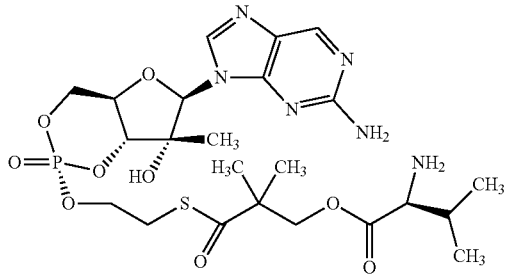

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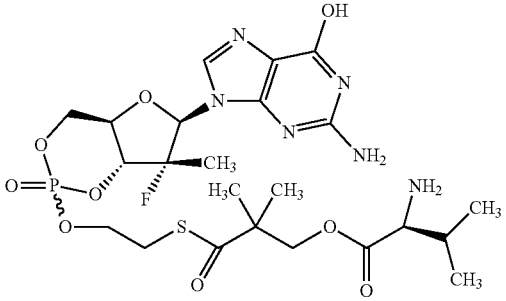

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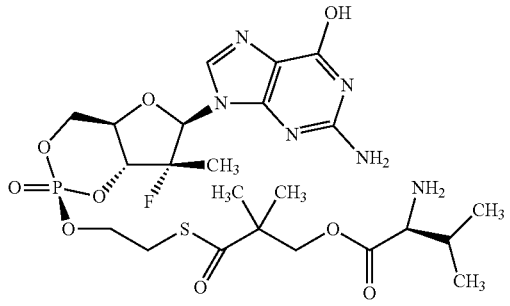

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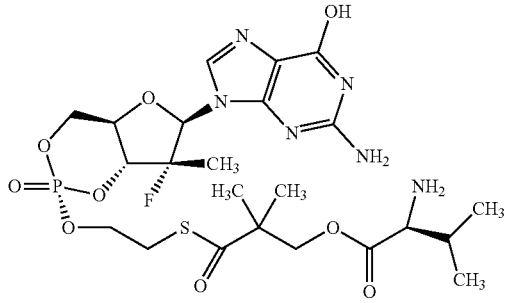

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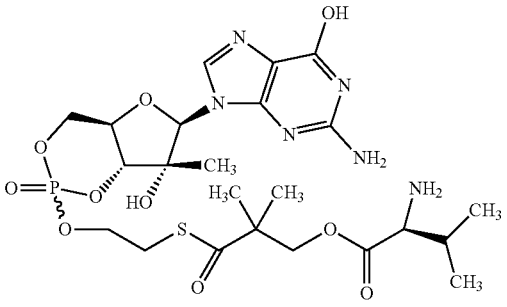

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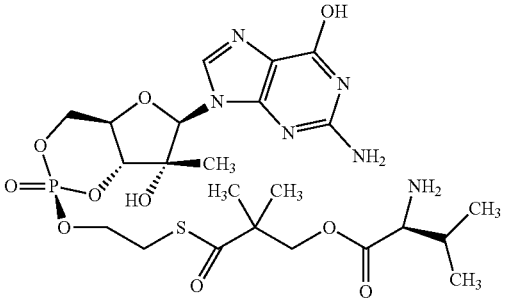

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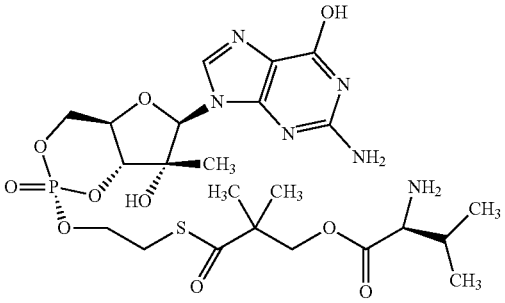

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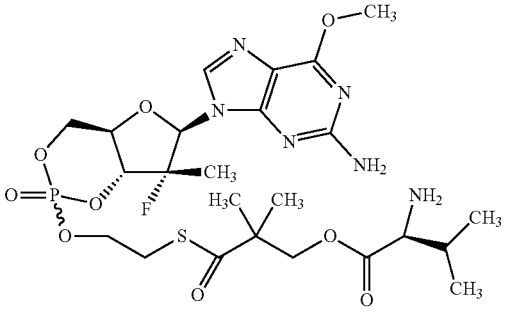

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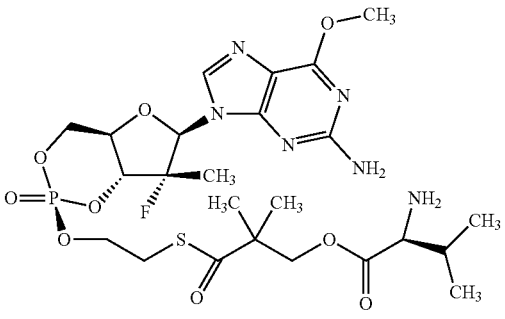

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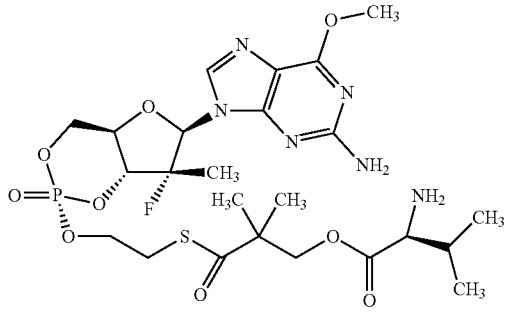

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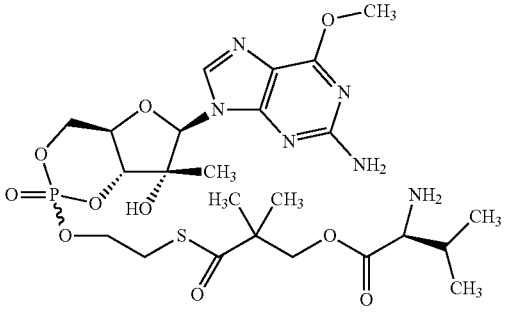

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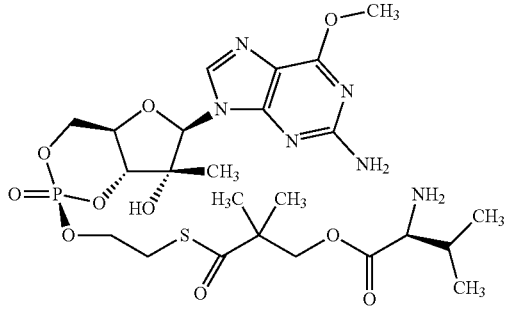

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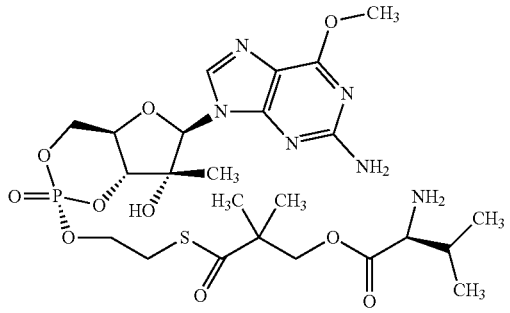

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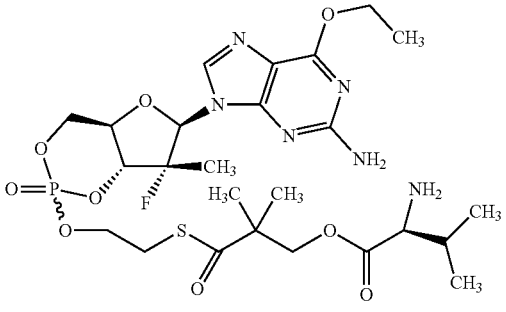

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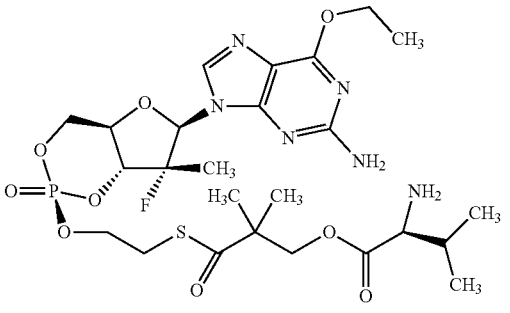

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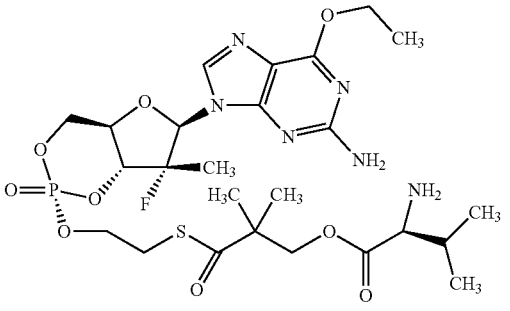

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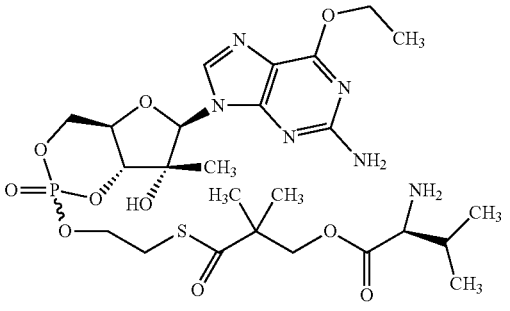

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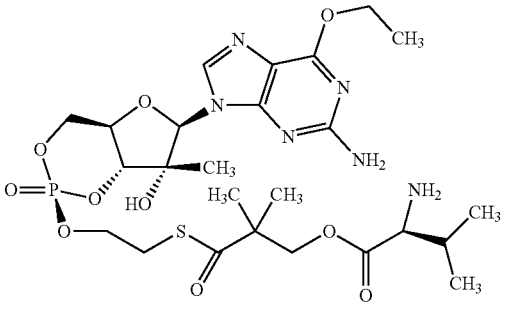

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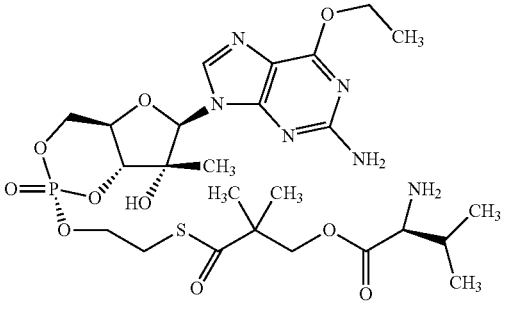

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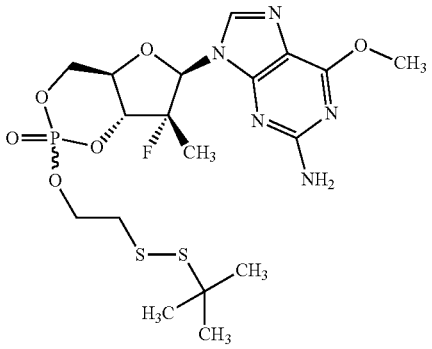

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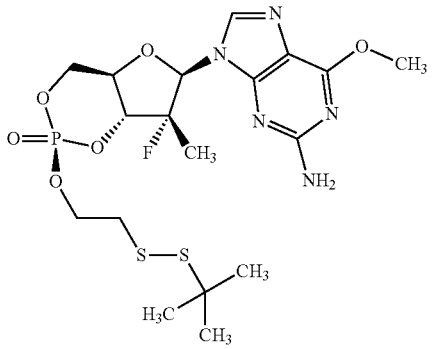

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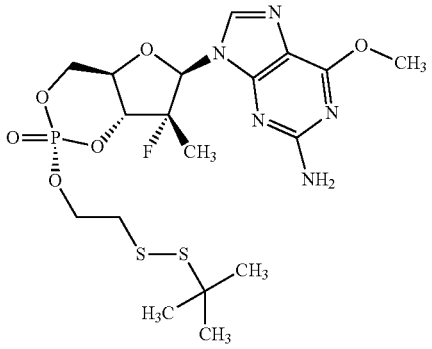

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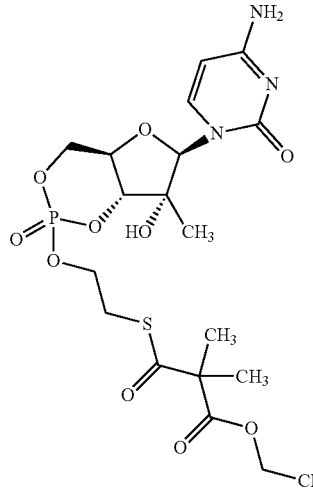

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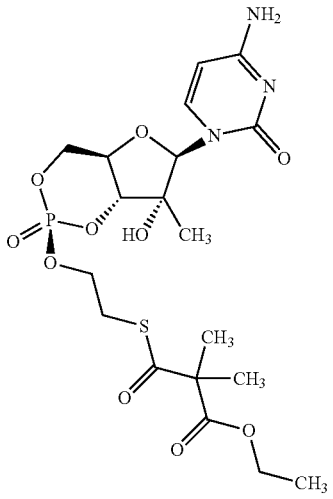

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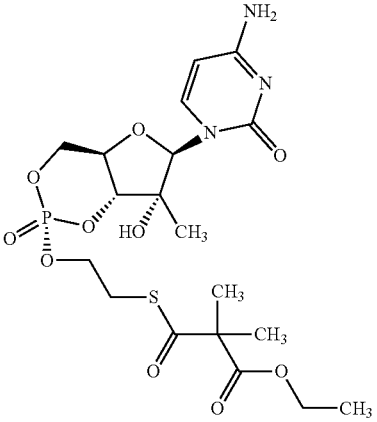

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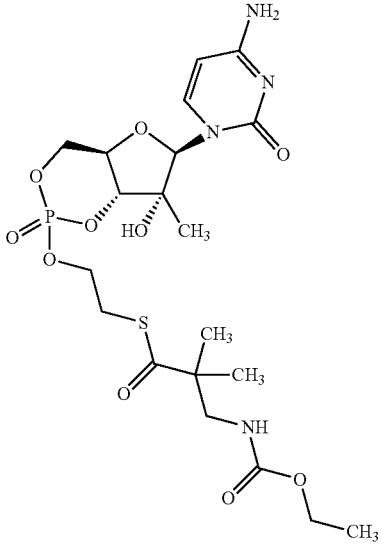

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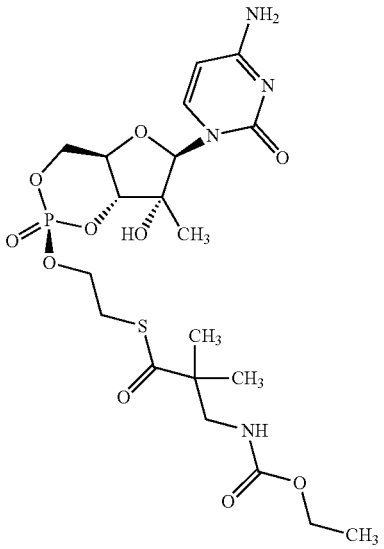

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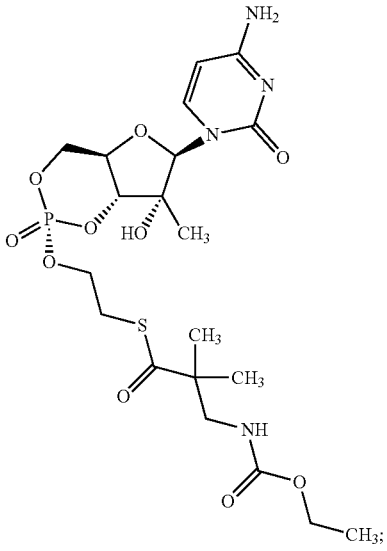


or pharmaceutically acceptable salts, solvates, stereoisomeric forms, tautomeric forms or polymorphic forms thereof.

In some embodiments, provided herein are:

(a) compounds as described herein, e.g., of Formula I-IXe or 1-67b, and pharmaceutically acceptable salts and compositions thereof;

(b) compounds as described herein, e.g., of Formula I-IXe or 1-67b, and pharmaceutically acceptable salts and compositions thereof for use in the treatment and/or prophylaxis of a liver disorder including Flaviviridae infection, especially in individuals diagnosed as having a Flaviviridae infection or being at risk of becoming infected by hepatitis C;

(c) processes for the preparation of compounds as described herein, e.g., of Formula I-IXe or 1-67b, as described in more detail elsewhere herein;

(d) pharmaceutical formulations comprising a compound as described herein, e.g., of Formula I-IXe or 1-67b, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent;

(e) pharmaceutical formulations comprising a compound as described herein, e.g., of Formula I-IXe or 1-67b, or a pharmaceutically acceptable salt thereof together with one or more other effective anti-HCV agents, optionally in a pharmaceutically acceptable carrier or diluent;

(f) a method for the treatment and/or prophylaxis of a host infected with Flaviviridae that includes the administration of an effective amount of a compound as described herein, e.g., of Formula I-IXe or 1-67b, its pharmaceutically acceptable salt or composition; or

(g) a method for the treatment and/or prophylaxis of a host infected with Flaviviridae that includes the administration of an effective amount of a compounds as described herein, e.g., of Formula I-IXe or 1-67b, its pharmaceutically acceptable salt or composition in combination and/or alternation with one or more effective anti-HCV agent.

Optically Active Compounds

It is appreciated that compounds provided herein have several chiral centers and may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that any racemic, optically-active, diastereomeric, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound provided herein, which possess the useful properties described herein is within the scope of the invention. It being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

In particular, since the 1' and 4' carbons of a nucleoside are chiral, their non-hydrogen substituents (the base and the CHOR groups, respectively) can be either cis (on the same side) or trans (on opposite sides) with respect to the sugar ring system. The four optical isomers therefore are represented by the following configurations (when orienting the sugar moiety in a horizontal plane such that the oxygen atom is in the back): cis (with both groups "up", which corresponds to the configuration of naturally occurring β-D nucleosides), cis (with both groups "down", which is a non-naturally occurring β-L configuration), trans (with the C2' substituent "up" and the C4' substituent "down"), and trans (with the C2' substituent "down" and the C4' substituent "up"). The "D-nucleosides" are cis nucleosides in a natural configuration and the "L-nucleosides" are cis nucleosides in the non-naturally occurring configuration.

Likewise, most amino acids are chiral (designated as L or D, wherein the L enantiomer is the naturally occurring configuration) and can exist as separate enantiomers.

Examples of methods to obtain optically active materials are known in the art, and include at least the following.

i) physical separation of crystals—a technique whereby macroscopic crystals of the individual enantiomers are manually separated. This technique can be used if crystals of the separate enantiomers exist, i.e., the material is a conglomerate, and the crystals are visually distinct;

ii) simultaneous crystallization—a technique whereby the individual enantiomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state;

iii) enzymatic resolutions—a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the enantiomers with an enzyme;

iv) enzymatic asymmetric synthesis—a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an enantiomerically pure or enriched synthetic precursor of the desired enantiomer;

v) chemical asymmetric synthesis—a synthetic technique whereby the desired enantiomer is synthesized from an

achiral precursor under conditions that produce asymmetry (i.e., chirality) in the product, which may be achieved using chiral catalysts or chiral auxiliaries;

vi) diastereomer separations—a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer;

vii) first- and second-order asymmetric transformations—a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer;

viii) kinetic resolutions—this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;

ix) enantiospecific synthesis from non-racemic precursors—a synthetic technique whereby the desired enantiomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;

x) chiral liquid chromatography—a technique whereby the enantiomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase. The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;

xi) chiral gas chromatography—a technique whereby the racemate is volatilized and enantiomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;

xii) extraction with chiral solvents—a technique whereby the enantiomers are separated by virtue of preferential dissolution of one enantiomer into a particular chiral solvent;

xiii) transport across chiral membranes—a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic chiral nature of the membrane which allows only one enantiomer of the racemate to pass through.

In some embodiments, compositions of 3',5'-cyclic phosphate prodrug compounds that are substantially free of a designated enantiomer of that compound. In certain embodiments, in the methods and compounds of this invention, the compounds are substantially free of enantiomers. In some embodiments, the composition includes that includes a compound that is at least 85, 90%, 95%, 98%, 99% to 100% by weight, of the compound, the remainder comprising other chemical species or enantiomers.

Isotopically Enriched Compounds

Also provided herein are isotopically enriched compounds, including but not limited to isotopically enriched 3',5'-cyclic phosphate prodrug compounds.

Isotopic enrichment (for example, deuteration) of pharmaceuticals to improve pharmacokinetics ("PK"), pharmacodynamics ("PD"), and toxicity profiles, has been demonstrated previously with some classes of drugs. See, for example, Lijinsky et. al., Food Cosmet. Toxicol., 20: 393 (1982); Lijinsky et. al., J. Nat. Cancer Inst., 69: 1127 (1982); Mangold et. al., Mutation Res. 308: 33 (1994); Gordon et. al., Drug Metab. Dispos., 15: 589 (1987); Zello et. al., Metabolism, 43: 487 (1994); Gately et. al., J. Nucl. Med., 27: 388 (1986); Wade D, Chem. Biol. Interact. 117: 191 (1999).

Isotopic enrichment of a drug can be used, for example, to (1) reduce or eliminate unwanted metabolites, (2) increase the half-life of the parent drug, (3) decrease the number of doses needed to achieve a desired effect, (4) decrease the amount of a dose necessary to achieve a desired effect, (5) increase the formation of active metabolites, if any are formed, and/or (6) decrees the production of deleterious metabolites in specific tissues and/or create a more effective drug and/or a safer drug for combination therapy, whether the combination therapy is intentional or not.

Replacement of an atom for one of its isotopes often will result in a change in the reaction rate of a chemical reaction. This phenomenon is known as the Kinetic Isotope Effect ("KIE"). For example, if a C—H bond is broken during a rate-determining step in a chemical reaction (i.e. the step with the highest transition state energy), substitution of a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect ("DKIE"). (See, e.g., Foster et al., Adv. Drug Res., vol. 14, pp. 1-36 (1985); Kushner et al., Can. J. Physiol. Pharmacol., vol. 77, pp. 79-88 (1999)).

The magnitude of the DKIE can be expressed as the ratio between the rates of a given reaction in which a C—H bond is broken, and the same reaction where deuterium is substituted for hydrogen. The DKIE can range from about 1 (no isotope effect) to very large numbers, such as 50 or more, meaning that the reaction can be fifty, or more, times slower when deuterium is substituted for hydrogen. High DKIE values may be due in part to a phenomenon known as tunneling, which is a consequence of the uncertainty principle. Tunneling is ascribed to the small mass of a hydrogen atom, and occurs because transition states involving a proton can sometimes form in the absence of the required activation energy. Because deuterium has more mass than hydrogen, it statistically has a much lower probability of undergoing this phenomenon.

Tritium ("T") is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as T_2O. Tritium decays slowly (half-life=12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level. Substitution of tritium ("T") for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects. Similarly, substitution of isotopes for other elements, including, but not limited to, ^{13}C or ^{14}C for carbon, ^{33}S, ^{34}S,

or ^{36}S for sulfur, ^{15}N for nitrogen, and ^{17}O or ^{18}O for oxygen, may lead to a similar kinetic isotope effect.

For example, the DKIE was used to decrease the hepatotoxicity of halothane by presumably limiting the production of reactive species such as trifluoroacetyl chloride. However, this method may not be applicable to all drug classes. For example, deuterium incorporation can lead to metabolic switching. The concept of metabolic switching asserts that xenogens, when sequestered by Phase I enzymes, may bind transiently and re-bind in a variety of conformations prior to the chemical reaction (e.g., oxidation). This hypothesis is supported by the relatively vast size of binding pockets in many Phase I enzymes and the promiscuous nature of many metabolic reactions. Metabolic switching can potentially lead to different proportions of known metabolites as well as altogether new metabolites. This new metabolic profile may impart more or less toxicity.

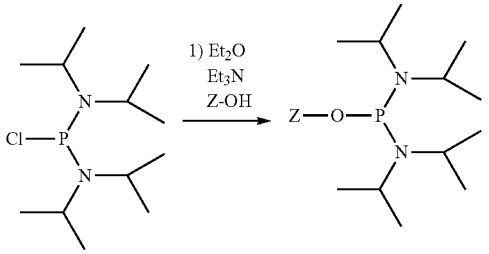
The animal body expresses a variety of enzymes for the purpose of eliminating foreign substances, such as therapeutic agents, from its circulation system. Examples of such enzymes include the cytochrome P450 enzymes ("CYPs"), esterases, proteases, reductases, dehydrogenases, and monoamine oxidases, to react with and convert these foreign substances to more polar intermediates or metabolites for renal excretion. Some of the most common metabolic reactions of pharmaceutical compounds involve the oxidation of a carbon-hydrogen (C—H) bond to either a carbon-oxygen (C—O) or carbon-carbon (C—C) pi-bond. The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, and acute and long-term toxicity profiles relative to the parent compounds. For many drugs, such oxidations are rapid. These drugs therefore often require the administration of multiple or high daily doses.

Therefore, isotopic enrichment at certain positions of a compound provided herein will produce a detectable KIE that will affect the pharmacokinetic, pharmacologic, and/or toxicological profiles of a compound provided herein in comparison with a similar compound having a natural isotopic composition.

Preparation of Compounds

The compounds provided herein can be prepared, isolated or obtained by any method apparent to those of skill in the art. Exemplary methods of preparation are described in detail in the examples below. In certain embodiments, compounds provided herein can be prepared according to either of Schemes 1a and 1b:

Scheme 1a



Intermediate 1

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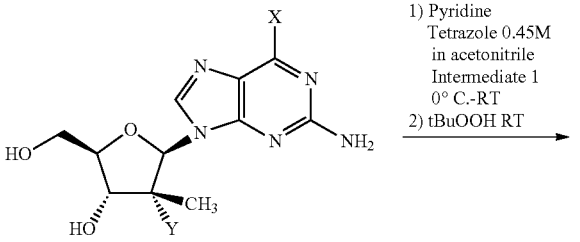
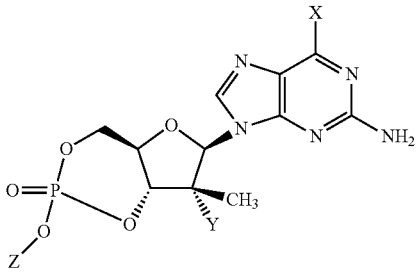
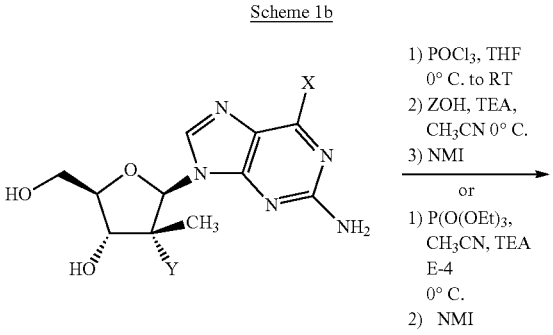
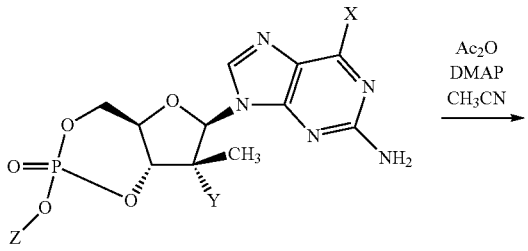




Compound 1: above
Compound 1a: Diastereomer 1
Compound 1b: Diastereomer 2

Scheme 1b





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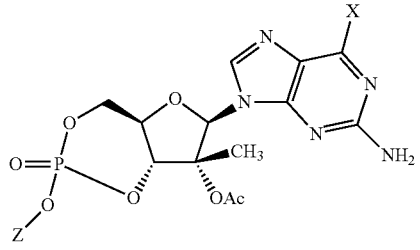

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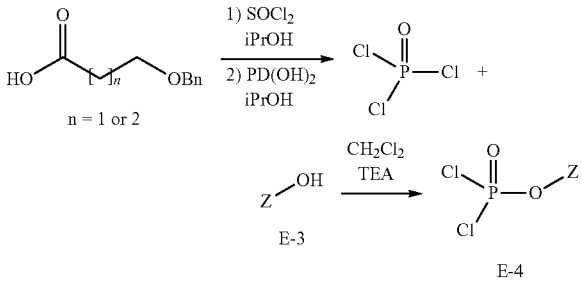


In certain embodiments, one or more protection or deprotection steps may be included in the methods of preparation described in Scheme 1.

Pharmaceutical Compositions and Methods of Administration

3',5'-cyclic phosphate prodrug compounds can be formulated into pharmaceutical compositions using methods available in the art and those disclosed herein. Any of the compounds disclosed herein can be provided in the appropriate pharmaceutical composition and be administered by a suitable route of administration.

The methods provided herein encompass administering pharmaceutical compositions containing at least one compound as described herein, including a compound of Formula I-IXe or 1-67b, if appropriate in the salt form, either used alone or in the form of a combination with one or more compatible and pharmaceutically acceptable carriers, such as diluents or adjuvants, or with another anti-HCV agent.

In certain embodiments, the second agent can be formulated or packaged with the compound provided herein. Of course, the second agent will only be formulated with the compound provided herein when, according to the judgment of those of skill in the art, such co-formulation should not interfere with the activity of either agent or the method of administration. In certain embodiments, the compound provided herein and the second agent are formulated separately. They can be packaged together, or packaged separately, for the convenience of the practitioner of skill in the art.

In clinical practice the active agents provided herein may be administered by any conventional route, in particular orally, parenterally, rectally or by inhalation (e.g. in the form of aerosols). In certain embodiments, the compound provided herein is administered orally.

Use may be made, as solid compositions for oral administration, of tablets, pills, hard gelatin capsules, powders or granules. In these compositions, the active product is mixed with one or more inert diluents or adjuvants, such as sucrose, lactose or starch.

These compositions can comprise substances other than diluents, for example a lubricant, such as magnesium stearate, or a coating intended for controlled release.

Use may be made, as liquid compositions for oral administration, of solutions which are pharmaceutically acceptable, suspensions, emulsions, syrups and elixirs containing inert diluents, such as water or liquid paraffin. These compositions can also comprise substances other than diluents, for example wetting, sweetening or flavoring products.

The compositions for parenteral administration can be emulsions or sterile solutions. Use may be made, as solvent or vehicle, of propylene glycol, a polyethylene glycol, vegetable oils, in particular olive oil, or injectable organic esters, for example ethyl oleate. These compositions can also contain adjuvants, in particular wetting, isotonizing, emulsifying, dispersing and stabilizing agents. Sterilization can be carried out in several ways, for example using a bacteriological filter, by radiation or by heating. They can also be prepared in the form of sterile solid compositions which can be dissolved at the time of use in sterile water or any other injectable sterile medium.

The compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active principle, excipients such as cocoa butter, semi-synthetic glycerides or polyethylene glycols.

The compositions can also be aerosols. For use in the form of liquid aerosols, the compositions can be stable sterile solutions or solid compositions dissolved at the time of use in apyrogenic sterile water, in saline or any other pharmaceutically acceptable vehicle. For use in the form of dry aerosols intended to be directly inhaled, the active principle is finely divided and combined with a water-soluble solid diluent or vehicle, for example dextran, mannitol or lactose.

In certain embodiments, a composition provided herein is a pharmaceutical composition or a single unit dosage form. Pharmaceutical compositions and single unit dosage forms provided herein comprise a prophylactically or therapeutically effective amount of one or more prophylactic or therapeutic agents (e.g., a compound provided herein, or other prophylactic or therapeutic agent), and a typically one or more pharmaceutically acceptable carriers or excipients. In a specific embodiment and in this context, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" includes a diluent, adjuvant (e.g., Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water can be used as a carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin.

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well-known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a subject and the specific active ingredients in the dosage form. The composition or single unit dosage form, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

Lactose free compositions provided herein can comprise excipients that are well known in the art and are listed, for example, in the U.S. Pharmocopia (USP) SP (XXI)/NF (XVI). In general, lactose free compositions comprise an active ingredient, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Exemplary lactose free dosage forms comprise an

active ingredient, microcrystalline cellulose, pre gelatinized starch, and magnesium stearate.

Further encompassed herein are anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long term storage in order to determine characteristics such as shelf life or the stability of formulations over time. See, e.g., Jens T. Carstensen, Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, NY, N.Y., 1995, pp. 379 80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine can be anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs, and strip packs.

Further provided are pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

The pharmaceutical compositions and single unit dosage forms can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Such compositions and dosage forms will contain a prophylactically or therapeutically effective amount of a prophylactic or therapeutic agent, in certain embodiments, in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the subject. The formulation should suit the mode of administration. In a certain embodiment, the pharmaceutical compositions or single unit dosage forms are sterile and in suitable form for administration to a subject, for example, an animal subject, such as a mammalian subject, for example, a human subject.

A pharmaceutical composition is formulated to be compatible with its intended route of administration. Examples of routes of administration include, but are not limited to, parenteral, e.g., intravenous, intradermal, subcutaneous, intramuscular, subcutaneous, oral, buccal, sublingual, inhalation, intranasal, transdermal, topical, transmucosal, intratumoral, intra-synovial and rectal administration. In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal or topical administration to human beings. In an embodiment, a pharmaceutical composition is formulated in accordance with routine procedures for subcutaneous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocamne to ease pain at the site of the injection.

Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a subject, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil in water emulsions, or a water in oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a subject; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a subject.

The composition, shape, and type of dosage forms provided herein will typically vary depending on their use. For example, a dosage form used in the initial treatment of viral infection may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the maintenance treatment of the same infection. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed herein will vary from one another will be readily apparent to those skilled in the art. See, e.g., Remington's Pharmaceutical Sciences, 20th ed., Mack Publishing, Easton Pa. (2000).

Generally, the ingredients of compositions are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

Typical dosage forms comprise a compound provided herein, or a pharmaceutically acceptable salt, solvate or hydrate thereof lie within the range of from about 0.1 mg to about 1000 mg per day, given as a single once-a-day dose in the morning or as divided doses throughout the day taken with food. Particular dosage forms can have about 0.1, 0.2, 0.3, 0.4, 0.5, 1.0, 2.0, 2.5, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 100, 200, 250, 500 or 1000 mg of the active compound.

Oral Dosage Forms

Pharmaceutical compositions that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, Remington's Pharmaceutical Sciences, 20th ed., Mack Publishing, Easton Pa. (2000).

In certain embodiments, the oral dosage forms are solid and prepared under anhydrous conditions with anhydrous ingredients, as described in detail herein. However, the scope

of the compositions provided herein extends beyond anhydrous, solid oral dosage forms. As such, further forms are described herein.

Typical oral dosage forms are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or non-aqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL PH 101, AVICEL PH 103 AVICEL RC 581, AVICEL PH 105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa.), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC 581. Suitable anhydrous or low moisture excipients or additives include AVICEL PH 103™ and Starch 1500 LM.

Disintegrants are used in the compositions to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB O SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

Delayed Release Dosage Forms

Active ingredients such as the compounds provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500; each of which is incorporated herein by reference in its entirety. Such dosage forms can be used to provide slow or controlled release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients provided herein. Thus encompassed herein are single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled release.

All controlled release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum

amount of time. Advantages of controlled release formulations include extended activity of the drug, reduced dosage frequency, and increased subject compliance. In addition, controlled release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

Most controlled release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

In certain embodiments, the drug may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In certain embodiments, a pump may be used (see, Sefton, *CRC Crit. Ref Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in a subject at an appropriate site determined by a practitioner of skill, i.e., thus requiring only a fraction of the systemic dose (see, e.g., Goodson, *Medical Applications of Controlled Release, vol.* 2, pp. 115-138 (1984)). Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)). The active ingredient can be dispersed in a solid inner matrix, e.g., polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, e.g., polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The active ingredient then diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active ingredient in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

Parenteral Dosage Forms

In certain embodiments, provided are parenteral dosage forms. Parenteral dosage forms can be administered to subjects by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses subjects' natural defenses against contaminants, parenteral dosage forms are typically, sterile or capable of being sterilized prior to administration to a subject. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms.

Transdermal, Topical & Mucosal Dosage Forms

Also provided are transdermal, topical, and mucosal dosage forms. Transdermal, topical, and mucosal dosage forms include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. See, e.g., *Remington's Pharmaceutical Sciences,* 16th, 18th and 20th eds., Mack Publishing, Easton Pa. (1980, 1990 & 2000); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels. Further, transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed herein are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane 1,3 diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form lotions, tinctures, creams, emulsions, gels or ointments, which are nontoxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. See, e.g., Remington's Pharmaceutical Sciences, 16th, 18th and 20th eds., Mack Publishing, Easton Pa. (1980, 1990 & 2000).

Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients provided. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or

dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery enhancing or penetration enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Dosage and Unit Dosage Forms

In human therapeutics, the doctor will determine the posology which he considers most appropriate according to a preventive or curative treatment and according to the age, weight, stage of the infection and other factors specific to the subject to be treated. In certain embodiments, doses are from about 1 to about 1000 mg per day for an adult, or from about 5 to about 250 mg per day or from about 10 to 50 mg per day for an adult. In certain embodiments, doses are from about 5 to about 400 mg per day or 25 to 200 mg per day per adult. In certain embodiments, dose rates of from about 50 to about 500 mg per day are also contemplated.

In further aspects, provided are methods of treating or preventing an HCV infection in a subject by administering, to a subject in need thereof, an effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof. The amount of the compound or composition which will be effective in the prevention or treatment of a disorder or one or more symptoms thereof will vary with the nature and severity of the disease or condition, and the route by which the active ingredient is administered. The frequency and dosage will also vary according to factors specific for each subject depending on the specific therapy (e.g., therapeutic or prophylactic agents) administered, the severity of the disorder, disease, or condition, the route of administration, as well as age, body, weight, response, and the past medical history of the subject. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

In certain embodiments, exemplary doses of a composition include milligram or microgram amounts of the active compound per kilogram of subject or sample weight (e.g., about 10 micrograms per kilogram to about 50 milligrams per kilogram, about 100 micrograms per kilogram to about 25 milligrams per kilogram, or about 100 microgram per kilogram to about 10 milligrams per kilogram). For compositions provided herein, in certain embodiments, the dosage administered to a subject is 0.140 mg/kg to 3 mg/kg of the subject's body weight, based on weight of the active compound. In certain embodiments, the dosage administered to a subject is between 0.20 mg/kg and 2.00 mg/kg, or between 0.30 mg/kg and 1.50 mg/kg of the subject's body weight.

In certain embodiments, the recommended daily dose range of a composition provided herein for the conditions described herein lie within the range of from about 0.1 mg to about 1000 mg per day, given as a single once-a-day dose or as divided doses throughout a day. In certain embodiments, the daily dose is administered twice daily in equally divided doses. In certain embodiments, a daily dose range should be from about 10 mg to about 200 mg per day, in other embodiments, between about 10 mg and about 150 mg per day, in further embodiments, between about 25 and about 100 mg per day. It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with subject response.

Different therapeutically effective amounts may be applicable for different diseases and conditions, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat or ameliorate such disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with the composition provided herein are also encompassed by the herein described dosage amounts and dose frequency schedules. Further, when a subject is administered multiple dosages of a composition provided herein, not all of the dosages need be the same. For example, the dosage administered to the subject may be increased to improve the prophylactic or therapeutic effect of the composition or it may be decreased to reduce one or more side effects that a particular subject is experiencing.

In certain embodiment, the dosage of the composition provided herein, based on weight of the active compound, administered to prevent, treat, manage, or ameliorate a disorder, or one or more symptoms thereof in a subject is 0.1 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 10 mg/kg, or 15 mg/kg or more of a subject's body weight. In another embodiment, the dosage of the composition or a composition provided herein administered to prevent, treat, manage, or ameliorate a disorder, or one or more symptoms thereof in a subject is a unit dose of 0.1 mg to 200 mg, 0.1 mg to 100 mg, 0.1 mg to 50 mg, 0.1 mg to 25 mg, 0.1 mg to 20 mg, 0.1 mg to 15 mg, 0.1 mg to 10 mg, 0.1 mg to 7.5 mg, 0.1 mg to 5 mg, 0.1 to 2.5 mg, 0.25 mg to 20 mg, 0.25 to 15 mg, 0.25 to 12 mg, 0.25 to 10 mg, 0.25 mg to 7.5 mg, 0.25 mg to 5 mg, 0.5 mg to 2.5 mg, 1 mg to 20 mg, 1 mg to 15 mg, 1 mg to 12 mg, 1 mg to 10 mg, 1 mg to 7.5 mg, 1 mg to 5 mg, or 1 mg to 2.5 mg.

In certain embodiments, treatment or prevention can be initiated with one or more loading doses of a compound or composition provided herein followed by one or more maintenance doses. In such embodiments, the loading dose can be, for instance, about 60 to about 400 mg per day, or about 100 to about 200 mg per day for one day to five weeks. The loading dose can be followed by one or more maintenance doses. In certain embodiments, each maintenance does is, independently, about from about 10 mg to about 200 mg per day, between about 25 mg and about 150 mg per day, or between about 25 and about 80 mg per day. Maintenance doses can be administered daily and can be administered as single doses, or as divided doses.

In certain embodiments, a dose of a compound or composition provided herein can be administered to achieve a steady-state concentration of the active ingredient in blood or serum of the subject. The steady-state concentration can be determined by measurement according to techniques available to those of skill or can be based on the physical characteristics of the subject such as height, weight and age. In certain embodiments, a sufficient amount of a compound or composition provided herein is administered to achieve a steady-state concentration in blood or serum of the subject of from about 300 to about 4000 ng/mL, from about 400 to about 1600 ng/mL, or from about 600 to about 1200 ng/mL. In some embodiments, loading doses can be administered to achieve steady-state blood or serum concentrations of about 1200 to about 8000 ng/mL, or about 2000 to about 4000 ng/mL for one to five days. In certain embodiments, maintenance doses can be administered to achieve a steady-state concentration in

blood or serum of the subject of from about 300 to about 4000 ng/mL, from about 400 to about 1600 ng/mL, or from about 600 to about 1200 ng/mL.

In certain embodiments, administration of the same composition may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same prophylactic or therapeutic agent may be repeated and the administration may be separated by at least at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

In certain aspects, provided herein are unit dosages comprising a compound, or a pharmaceutically acceptable salt thereof, in a form suitable for administration. Such forms are described in detail herein. In certain embodiments, the unit dosage comprises 1 to 1000 mg, 5 to 250 mg or 10 to 50 mg active ingredient. In particular embodiments, the unit dosages comprise about 1, 5, 10, 25, 50, 100, 125, 250, 500 or 1000 mg active ingredient. Such unit dosages can be prepared according to techniques familiar to those of skill in the art.

The dosages of the second agents are to be used in the combination therapies provided herein. In certain embodiments, dosages lower than those which have been or are currently being used to prevent or treat HCV infection are used in the combination therapies provided herein. The recommended dosages of second agents can be obtained from the knowledge of those of skill. For those second agents that are approved for clinical use, recommended dosages are described in, for example, Hardman et al., eds., 1996, Goodman & Gilman's The Pharmacological Basis Of Basis Of Therapeutics 9th Ed, Mc-Graw-Hill, New York; Physician's Desk Reference (PDR) 57th Ed., 2003, Medical Economics Co., Inc., Montvale, N.J., which are incorporated herein by reference in its entirety.

In various embodiments, the therapies (e.g., a compound provided herein and the second agent) are administered less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours apart. In various embodiments, the therapies are administered no more than 24 hours apart or no more than 48 hours apart. In certain embodiments, two or more therapies are administered within the same patient visit. In other embodiments, the compound provided herein and the second agent are administered concurrently.

In other embodiments, the compound provided herein and the second agent are administered at about 2 to 4 days apart, at about 4 to 6 days apart, at about 1 week part, at about 1 to 2 weeks apart, or more than 2 weeks apart.

In certain embodiments, administration of the same agent may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same agent may be repeated and the administration may be separated by at least at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

In certain embodiments, a compound provided herein and a second agent are administered to a patient, for example, a mammal, such as a human, in a sequence and within a time interval such that the compound provided herein can act together with the other agent to provide an increased benefit than if they were administered otherwise. For example, the second active agent can be administered at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. In certain embodiments, the compound provided herein and the second active agent exert their effect at times which overlap. Each second active agent can be administered separately, in any appropriate form and by any suitable route. In other embodiments, the compound provided herein is administered before, concurrently or after administration of the second active agent.

In certain embodiments, the compound provided herein and the second agent are cyclically administered to a patient. Cycling therapy involves the administration of a first agent (e.g., a first prophylactic or therapeutic agents) for a period of time, followed by the administration of a second agent and/or third agent (e.g., a second and/or third prophylactic or therapeutic agents) for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improve the efficacy of the treatment.

In certain embodiments, the compound provided herein and the second active agent are administered in a cycle of less than about 3 weeks, about once every two weeks, about once every 10 days or about once every week. One cycle can comprise the administration of a compound provided herein and the second agent by infusion over about 90 minutes every cycle, about 1 hour every cycle, about 45 minutes every cycle. Each cycle can comprise at least 1 week of rest, at least 2 weeks of rest, at least 3 weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

In other embodiments, courses of treatment are administered concurrently to a patient, i.e., individual doses of the second agent are administered separately yet within a time interval such that the compound provided herein can work together with the second active agent. For example, one component can be administered once per week in combination with the other components that can be administered once every two weeks or once every three weeks. In other words, the dosing regimens are carried out concurrently even if the therapeutics are not administered simultaneously or during the same day.

The second agent can act additively or synergistically with the compound provided herein. In certain embodiments, the compound provided herein is administered concurrently with one or more second agents in the same pharmaceutical composition. In another embodiment, a compound provided herein is administered concurrently with one or more second agents in separate pharmaceutical compositions. In still another embodiment, a compound provided herein is administered prior to or subsequent to administration of a second agent. Also contemplated are administration of a compound provided herein and a second agent by the same or different routes of administration, e.g., oral and parenteral. In certain embodiments, when the compound provided herein is administered concurrently with a second agent that potentially pro-

duces adverse side effects including, but not limited to, toxicity, the second active agent can advantageously be administered at a dose that falls below the threshold that the adverse side effect is elicited.

Kits

Also provided are kits for use in methods of treatment of a liver disorder such as HCV infections. The kits can include a compound or composition provided herein, a second agent or composition, and instructions providing information to a health care provider regarding usage for treating the disorder. Instructions may be provided in printed form or in the form of an electronic medium such as a floppy disc, CD, or DVD, or in the form of a website address where such instructions may be obtained. A unit dose of a compound or composition provided herein, or a second agent or composition, can include a dosage such that when administered to a subject, a therapeutically or prophylactically effective plasma level of the compound or composition can be maintained in the subject for at least 1 days. In some embodiments, a compound or composition can be included as a sterile aqueous pharmaceutical composition or dry powder (e.g., lyophilized) composition.

In some embodiments, suitable packaging is provided. As used herein, "packaging" includes a solid matrix or material customarily used in a system and capable of holding within fixed limits a compound provided herein and/or a second agent suitable for administration to a subject. Such materials include glass and plastic (e.g., polyethylene, polypropylene, and polycarbonate) bottles, vials, paper, plastic, and plastic-foil laminated envelopes and the like. If e-beam sterilization techniques are employed, the packaging should have sufficiently low density to permit sterilization of the contents.

Methods of Use

In certain embodiments, provided herein are methods for the treatment and/or prophylaxis of a host infected with Flaviviridae that includes the administration of an effective amount of a compounds provided herein, or a pharmaceutically acceptable salt thereof. In certain embodiments, provided herein are methods for treating an HCV infection in a subject. In certain embodiments, the methods encompass the step of administering to the subject in need thereof an amount of a compound effective for the treatment or prevention of an HCV infection in combination with a second agent effective for the treatment or prevention of the infection. The compound can be any compound as described herein, and the second agent can be any second agent described in the art or herein. In certain embodiments, the compound is in the form of a pharmaceutical composition or dosage form, as described elsewhere herein.

Flaviviridae that can be treated are discussed generally in Fields Virology, Editors: Fields, B. N., Knipe, D. M., and Howley, P. M., Lippincott-Raven Publishers, Philadelphia, Pa., Chapter 31, 1996. In a particular embodiment of the invention, the Flaviviridae is HCV. In an alternate embodiment of the invention, the Flaviviridae is a flavivirus or pestivirus. Specific flaviviruses include, without limitation: Absettarov, Alfuy, Apoi, Aroa, Bagaza, Banzi, Bouboui, Bussuquara, Cacipacore, Carey Island, Dakar bat, Dengue 1, Dengue 2, Dengue 3, Dengue 4, Edge Hill, Entebbe bat, Gadgets Gully, Hanzalova, Hypr, Ilheus, Israel turkey meningoencephalitis, Japanese encephalitis, Jugra, Jutiapa, Kadam, Karshi, Kedougou, Kokobera, Koutango, Kumlinge, Kunjin, Kyasanur Forest disease, Langat, Louping ill, Meaban, Modoc, Montana myotis leukoencephalitis, Murray valley encephalitis, Naranjal, Negishi, Ntaya, Omsk hemorrhagic fever, Phnom-Penh bat, Powassan, Rio Bravo, Rocio, Royal Farm, Russian spring-summer encephalitis, Saboya, St. Louis encephalitis, Sal Vieja, San Perlita, Saumarez Reef, Sepik, Sokuluk, Spondweni, Stratford, Tembusu, Tyuleniy, Uganda S, Usutu, Wesselsbron, West Nile, Yaounde, Yellow fever, and Zika.

Pestiviruses that can be treated are discussed generally in Fields Virology, Editors: Fields, B. N., Knipe, D. M., and Howley, P. M., Lippincott-Raven Publishers, Philadelphia, Pa., Chapter 33, 1996. Specific pestiviruses include, without limitation: bovine viral diarrhea virus ("BVDV"), classical swine fever virus ("CSFV," also called hog cholera virus), and border disease virus ("BDV").

In certain embodiments, the subject can be any subject infected with, or at risk for infection with, HCV. Infection or risk for infection can be determined according to any technique deemed suitable by the practitioner of skill in the art. In certain embodiments, subjects are humans infected with HCV.

In certain embodiments, the subject has never received therapy or prophylaxis for an HCV infection. In further embodiments, the subject has previously received therapy or prophylaxis for an HCV infection. For instance, in certain embodiments, the subject has not responded to an HCV therapy. For example, under current interferon therapy, up to 50% or more HCV subjects do not respond to therapy. In certain embodiments, the subject can be a subject that received therapy but continued to suffer from viral infection or one or more symptoms thereof. In certain embodiments, the subject can be a subject that received therapy but failed to achieve a sustained virologic response. In certain embodiments, the subject has received therapy for an HCV infection but has failed to show, for example, a 2 $\log_{10}$ decline in HCV RNA levels after 12 weeks of therapy. It is believed that subjects who have not shown more than 2 $\log_{10}$ reduction in serum HCV RNA after 12 weeks of therapy have a 97-100% chance of not responding.

In certain embodiments, the subject is a subject that discontinued an HCV therapy because of one or more adverse events associated with the therapy. In certain embodiments, the subject is a subject where current therapy is not indicated. For instance, certain therapies for HCV are associated with neuropsychiatric events. Interferon (IFN)-alfa plus ribavirin is associated with a high rate of depression. Depressive symptoms have been linked to a worse outcome in a number of medical disorders. Life-threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, relapse of drug addiction/overdose, and aggressive behavior have occurred in subjects with and without a previous psychiatric disorder during HCV therapy. Interferon-induced depression is a limitation for the treatment of chronic hepatitis C, especially for subjects with psychiatric disorders. Psychiatric side effects are common with interferon therapy and responsible for about 10% to 20% of discontinuations of current therapy for HCV infection.

Accordingly, provided are methods of treating or preventing an HCV infection in subjects where the risk of neuropsychiatric events, such as depression, contraindicates treatment with current HCV therapy. In certain embodiments, provided are methods of treating or preventing HCV infection in subjects where a neuropsychiatric event, such as depression, or risk of such indicates discontinuation of treatment with current HCV therapy. Further provided are methods of treating or preventing HCV infection in subjects where a neuropsychiatric event, such as depression, or risk of such indicates dose reduction of current HCV therapy.

Current therapy is also contraindicated in subjects that are hypersensitive to interferon or ribavirin, or both, or any other component of a pharmaceutical product for administration of

interferon or ribavirin. Current therapy is not indicated in subjects with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia) and other subjects at risk from the hematologic side effects of current therapy. Common hematologic side effects include bone marrow suppression, neutropenia and thrombocytopenia. Furthermore, ribavirin is toxic to red blood cells and is associated with hemolysis. Accordingly, in certain embodiments, provided are methods of treating or preventing HCV infection in subjects hypersensitive to interferon or ribavirin, or both, subjects with a hemoglobinopathy, for instance thalassemia major subjects and sickle-cell anemia subjects, and other subjects at risk from the hematologic side effects of current therapy.

In certain embodiments, the subject has received an HCV therapy and discontinued that therapy prior to administration of a method provided herein. In further embodiments, the subject has received therapy and continues to receive that therapy along with administration of a method provided herein. The methods can be co-administered with other therapy for HBC and/or HCV according to the judgment of one of skill in the art. In certain embodiments, the methods or compositions provided herein can be co-administered with a reduced dose of the other therapy for HBC and/or HCV.

In certain embodiments, provided are methods of treating a subject that is refractory to treatment with interferon. For instance, in some embodiments, the subject can be a subject that has failed to respond to treatment with one or more agents selected from the group consisting of interferon, interferon α, pegylated interferon α, interferon plus ribavirin, interferon α plus ribavirin and pegylated interferon α plus ribavirin. In some embodiments, the subject can be a subject that has responded poorly to treatment with one or more agents selected from the group consisting of interferon, interferon α, pegylated interferon α, interferon plus ribavirin, interferon α plus ribavirin and pegylated interferon α plus ribavirin. A pro-drug form of ribavirin, such as taribavirin, may also be used.

In certain embodiments, the subject has, or is at risk for, co-infection of HCV with HIV. For instance, in the United States, 30% of HIV subjects are co-infected with HCV and evidence indicates that people infected with HIV have a much more rapid course of their hepatitis C infection. Maier and Wu, 2002, *World J Gastroenterol* 8:577-57. The methods provided herein can be used to treat or prevent HCV infection in such subjects. It is believed that elimination of HCV in these subjects will lower mortality due to end-stage liver disease. Indeed, the risk of progressive liver disease is higher in subjects with severe AIDS-defining immunodeficiency than in those without. See, e.g., Lesens et al., 1999, *J Infect Dis* 179:1254-1258. In certain embodiments, compounds provided herein have been shown to suppress HIV in HIV subjects. Thus, in certain embodiments, provided are methods of treating or preventing HIV infection and HCV infection in subjects in need thereof.

In certain embodiments, the compounds or compositions are administered to a subject following liver transplant. Hepatitis C is a leading cause of liver transplantation in the U.S., and many subjects that undergo liver transplantation remain HCV positive following transplantation. In certain embodiments, provided are methods of treating such recurrent HCV subjects with a compound or composition provided herein. In certain embodiments, provided are methods of treating a subject before, during or following liver transplant to prevent recurrent HCV infection.

Assay Methods

Compounds can be assayed for HCV activity according to any assay known to those of skill in the art.

Further, compounds can be assayed for accumulation in liver cells of a subject according to any assay known to those of skill in the art. In certain embodiments, a compound can be administered to the subject, and a liver cell of the subject can be assayed for the compound or a derivative thereof, e.g. a nucleoside, nucleoside phosphate or nucleoside triphosphate derivative thereof.

In certain embodiments, a 3',5'-cyclic phosphate prodrug compound is administered to cells, such as liver cells, in vivo or in vitro, and the nucleoside triphosphate levels delivered intracellularly are measured, to indicate delivery of the compound and triphosphorylation in the cell. The levels of intracellular nucleoside triphosphate can be measured using analytical techniques known in the art. Methods of detecting ddATP are described herein below by way of example, but other nucleoside triphosphates can be readily detected using the appropriate controls, calibration samples and assay techniques.

In certain embodiments, ddATP concentrations are measured in a sample by comparison to calibration standards made from control samples. The ddATP concentrations in a sample can be measured using an analytical method such as HPLC LC MS. In certain embodiments, a test sample is compared to a calibration curve created with known concentrations of ddATP to thereby obtain the concentration of that sample.

In certain embodiments, the samples are manipulated to remove impurities such as salts (Na^+, K^+, etc.) before analysis. In certain embodiments, the lower limit of quantitation is about ~0.2 pmol/mL for hepatocyte cellular extracts particularly where reduced salt is present.

In certain embodiments, the method allows successfully measuring triphosphate nucleotides formed at levels of 1-10,000 pmol per million cells in e.g. cultured hepatocytes and HepG2 cells.

Second Therapeutic Agents

In certain embodiments, the compounds and compositions provided herein are useful in methods of treatment of a liver disorder, that comprise further administration of a second agent effective for the treatment of the disorder, such as HCV infection in a subject in need thereof. The second agent can be any agent known to those of skill in the art to be effective for the treatment of the disorder, including those currently approved by the FDA.

In certain embodiments, a compound provided herein is administered in combination with one second agent. In further embodiments, a second agent is administered in combination with two second agents. In still further embodiments, a second agent is administered in combination with two or more second agents.

As used herein, the term "in combination" includes the use of more than one therapy (e.g., one or more prophylactic and/or therapeutic agents). The use of the term "in combination" does not restrict the order in which therapies (e.g., prophylactic and/or therapeutic agents) are administered to a subject with a disorder. A first therapy (e.g., a prophylactic or therapeutic agent such as a compound provided herein) can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks,

8 weeks, or 12 weeks after) the administration of a second therapy (e.g., a prophylactic or therapeutic agent) to a subject with a disorder.

As used herein, the term "synergistic" includes a combination of a compound provided herein and another therapy (e.g., a prophylactic or therapeutic agent) which has been or is currently being used to prevent, manage or treat a disorder, which is more effective than the additive effects of the therapies. A synergistic effect of a combination of therapies (e.g., a combination of prophylactic or therapeutic agents) permits the use of lower dosages of one or more of the therapies and/or less frequent administration of said therapies to a subject with a disorder. The ability to utilize lower dosages of a therapy (e.g., a prophylactic or therapeutic agent) and/or to administer said therapy less frequently reduces the toxicity associated with the administration of said therapy to a subject without reducing the efficacy of said therapy in the prevention or treatment of a disorder). In addition, a synergistic effect can result in improved efficacy of agents in the prevention or treatment of a disorder. Finally, a synergistic effect of a combination of therapies (e.g., a combination of prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of either therapy alone.

The active compounds provided herein can be administered in combination or alternation with another therapeutic agent, in particular an anti-HCV agent. In combination therapy, effective dosages of two or more agents are administered together, whereas in alternation or sequential-step therapy, an effective dosage of each agent is administered serially or sequentially. The dosages given will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. In certain embodiments, an anti-HCV (or anti-pestivirus or anti-flavivirus) compound that exhibits an EC_{50} of 10-15 μM. In certain embodiments, less than 1-5 μM, is desirable.

It has been recognized that drug-resistant variants of flaviviruses, pestiviruses or HCV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for an enzyme used in viral replication. The efficacy of a drug against the viral infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principle drug. Alternatively, the pharmacokinetics, biodistribution or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

Any of the viral treatments described in the Background of the Invention can be used in combination or alternation with the compounds described in this specification. Non-limiting examples of second agents include:

HCV Protease inhibitors: Examples include Medivir HCV Protease Inhibitor (HCV-PI or TMC435) (Medivir/Tibotec); MK-7009 (Merck), RG7227 (ITMN-191) (Roche/Pharmasset/InterMune), boceprevir (SCH 503034) (Schering), SCH 446211 (Schering), narlaprevir SCH900518 (Schering/Merck), ABT-450 (Abbott/Enanta), ACH-1625 (Achillion), BI 201335 (Boehringer Ingelheim), PHX1766 (Phenomix), VX-500 (Vertex) and telaprevir (VX-950) (Vertex). Further examples of protease inhibitors include substrate-based NS3 protease inhibitors (Attwood et al., Antiviral peptide derivatives, PCT WO 98/22496, 1998; Attwood et al., *Antiviral Chemistry and Chemotherapy* 1999, 10, 259-273; Attwood et al., Preparation and use of amino acid derivatives as anti-viral agents, German Patent Pub. DE 19914474; Tung et al., Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease, PCT WO 98/17679), including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an electrophile such as a boronic acid or phosphonate (Llinas-Brunet et al, Hepatitis C inhibitor peptide analogues, PCT WO 99/07734); Non-substrate-based NS3 protease inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives (Sudo K. et al., *Biochemical and Biophysical Research Communications,* 1997, 238, 643-647; Sudo K. et al., *Antiviral Chemistry and Chemotherapy,* 1998, 9, 186), including RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a para-phenoxyphenyl group; and Sch 68631, a phenanthrenequinone, an HCV protease inhibitor (Chu M. et al., *Tetrahedron Letters* 37:7229-7232, 1996).

SCH 351633, isolated from the fungus *Penicillium griseofulvum*, was identified as a protease inhibitor (Chu M. et al., *Bioorganic and Medicinal Chemistry Letters* 9:1949-1952). Eglin c, isolated from leech, is a potent inhibitor of several serine proteases such as *S. griseus* proteases A and B, α-chymotrypsin, chymase and subtilisin. Qasim M. A. et al., *Biochemistry* 36:1598-1607, 1997.

U.S. patents disclosing protease inhibitors for the treatment of HCV include, for example, U.S. Pat. No. 6,004,933 to Spruce et al., which discloses a class of cysteine protease inhibitors for inhibiting HCV endopeptidase 2; U.S. Pat. No. 5,990,276 to Zhang et al., which discloses synthetic inhibitors of hepatitis C virus NS3 protease; U.S. Pat. No. 5,538,865 to Reyes et a; WO 02/008251 to Corvas International, Inc., and U.S. Pat. No. 7,169,760, US2005/176648, WO 02/08187 and WO 02/008256 to Schering Corporation. HCV inhibitor tripeptides are disclosed in U.S. Pat. Nos. 6,534,523, 6,410,531, and 6,420,380 to Boehringer Ingelheim and WO 02/060926 to Bristol Myers Squibb. Diaryl peptides as NS3 serine protease inhibitors of HCV are disclosed in WO 02/48172 and U.S. Pat. No. 6,911,428 to Schering Corporation. Imidazoleidinones as NS3 serine protease inhibitors of HCV are disclosed in WO 02/08198 and U.S. Pat. No. 6,838,475 to Schering Corporation and WO 02/48157 and U.S. Pat. No. 6,727,366 to Bristol Myers Squibb. WO 98/17679 and U.S. Pat. No. 6,265,380 to Vertex Pharmaceuticals and WO 02/48116 and U.S. Pat. No. 6,653,295 to Bristol Myers Squibb also disclose HCV protease inhibitors. Further examples of HCV serine protease inhibitors are provided in U.S. Pat. No. 6,872,805 (Bristol-Myers Squibb); WO 2006000085 (Boehringer Ingelheim); U.S. Pat. No. 7,208,600 (Vertex); US 2006/0046956 (Schering-Plough); WO 2007/001406 (Chiron); US 2005/0153877; WO 2006/119061 (Merck); WO 00/09543 (Boehringer Ingelheim), U.S. Pat. No. 6,323,180 (Boehringer Ingelheim) WO 03/064456 (Boehringer Ingelheim), U.S. Pat. No. 6,642,204 (Boehringer Ingelheim), WO 03/064416 (Boehringer Ingelheim), U.S. Pat. No. 7,091,184 (Boehringer Ingelheim), WO 03/053349 (Bristol-Myers Squibb), U.S. Pat. No. 6,867,185, WO 03/099316 (Bristol-Myers Squibb), U.S. Pat. No. 6,869,964, WO 03/099274 (Bristol-Myers Squibb), U.S. Pat. No. 6,995,174, WO 2004/032827 (Bristol-Myers Squibb), U.S. Pat. No. 7,041,698, WO 2004/043339 and U.S. Pat. No. 6,878,722 (Bristol-Myers Squibb).

Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein

and NS5A/5B substrate (Sudo K. et al., *Antiviral Research,* 1996, 32, 9-18), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193;

Thiazolidines and benzanilides identified in Kakiuchi N. et al., J. EBS Letters 421, 217-220; Takeshita N. et al., *Analytical Biochemistry,* 1997, 247, 242-246;

A phenanthrenequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of *Streptomyces* sp., SCH 68631 (Chu M. et al., *Tetrahedron Letters,* 1996, 37, 7229-7232), and SCH 351633, isolated from the fungus *Penicillium griseofulvum*, which demonstrates activity in a scintillation proximity assay (Chu M. et al., *Bioorganic and Medicinal Chemistry Letters* 9, 1949-1952);

Helicase inhibitors (Diana G. D. et al., Compounds, compositions and methods for treatment of hepatitis C, U.S. Pat. No. 5,633,358; Diana G. D. et al., Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment of hepatitis C, PCT WO 97/36554);

HCV polymerase inhibitors, including nucleoside and non-nucleoside polymerase inhibitors, such as ribavirin, viramidine, clemizole, filibuvir (PF-00868554), HCV POL, NM 283 (valopicitabine), MK-0608, 7-Fluoro-MK-0608, MK-3281, IDX-375, ABT-072, ABT-333, ANA598, BI 207127, GS 9190, PSI-6130, R1626, PSI-6206, PSI-938, PSI-7851, PSI-7977, RG1479, RG7128, HCV-796 VCH-759 or VCH-916.

Gliotoxin (Ferrari R. et al., *Journal of Virology,* 1999, 73, 1649-1654), and the natural product cerulenin (Lohmann V. et al., *Virology,* 1998, 249, 108-118);

Interfering RNA (iRNA) based antivirals, including short interfering RNA (siRNA) based antivirals, such as Sirna-034 and others described in International Patent Publication Nos. WO/03/070750 and WO 2005/012525, and US Patent Publication No. US 2004/0209831.

Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the 5' noncoding region (NCR) of the virus (Alt M. et al., *Hepatology,* 1995, 22, 707-717), or nucleotides 326-348 comprising the 3' end of the NCR and nucleotides 371-388 located in the core coding region of the HCV RNA (Alt M. et al., *Archives of Virology,* 1997, 142, 589-599; Galderisi U. et al., *Journal of Cellular Physiology,* 1999, 181, 251-257);

Inhibitors of IRES-dependent translation (Ikeda N et al., Agent for the prevention and treatment of hepatitis C, Japanese Patent Pub. JP-08268890; Kai Y. et al., Prevention and treatment of viral diseases, Japanese Patent Pub. JP-10101591);

HCV entry inhibitors, such as celgosivir (MK-3253) (MIGENIX Inc.), SP-30 (Samaritan Pharmaceuticals), ITX4520 (iTherX), ITX5061 (iTherX), PRO-206 (Progenics Pharmaceuticals) and other entry inhibitors by Progenics Pharmaceuticals, e.g., as disclosed in U.S. Patent Publication No. 2006/0198855.

Ribozymes, such as nuclease-resistant ribozymes (Maccjak, D. J. et al., *Hepatology* 1999, 30, abstract 995) and those disclosed in U.S. Pat. No. 6,043,077 to Barber et al., and U.S. Pat. Nos. 5,869,253 and 5,610,054 to Draper et al.; and

Nucleoside analogs have also been developed for the treatment of Flaviviridae infections.

In certain embodiments, the compounds provided herein can be administered in combination with any of the compounds described by Idenix Pharmaceuticals in International Publication Nos. WO 01/90121, WO 01/92282, WO 2004/003000, 2004/002422 and WO 2004/002999.

Other patent applications disclosing the use of certain nucleoside analogs that can be used as second agents to treat hepatitis C virus include: PCT/CA00/01316 (WO 01/32153; filed Nov. 3, 2000) and PCT/CA01/00197 (WO 01/60315; filed Feb. 19, 2001) filed by BioChem Pharma, Inc. (now Shire Biochem, Inc.); PCT/US02/01531 (WO 02/057425; filed Jan. 18, 2002); PCT/US02/03086 (WO 02/057287; filed Jan. 18, 2002); U.S. Pat. Nos. 7,202,224; 7,125,855; 7,105,499 and 6,777,395 by Merck & Co., Inc.; PCT/EP01/09633 (WO 02/18404; published Aug. 21, 2001); US 2006/0040890; 2005/0038240; 2004/0121980; U.S. Pat. No. 6,846,810; U.S. Pat. No. 6,784,166 and U.S. Pat. No. 6,660,721 by Roche; PCT Publication Nos. WO 01/79246 (filed Apr. 13, 2001), WO 02/32920 (filed Oct. 18, 2001) and WO 02/48165; US 2005/0009737; US 2005/0009737; U.S. Pat. No. 7,094,770 and U.S. Pat. No. 6,927,291 by Pharmasset, Ltd.

Further compounds that can be used as second agents to treat hepatitis C virus are disclosed in PCT Publication No. WO 99/43691 to Emory University, entitled "2'-Fluoronucleosides". The use of certain 2'-fluoronucleosides to treat HCV is disclosed.

Other compounds that can be used as second agents include 1-amino-alkylcyclohexanes (U.S. Pat. No. 6,034,134 to Gold et al.), alkyl lipids (U.S. Pat. No. 5,922,757 to Chojkier et al.), vitamin E and other antioxidants (U.S. Pat. No. 5,922,757 to Chojkier et al.), squalene, amantadine, bile acids (U.S. Pat. No. 5,846,964 to Ozeki et al.), N-(phosphonoacetyl)-L-aspartic acid, (U.S. Pat. No. 5,830,905 to Diana et al.), benzenedicarboxamides (U.S. Pat. No. 5,633,388 to Diana et al.), polyadenylic acid derivatives (U.S. Pat. No. 5,496,546 to Wang et al.), 2',3'-dideoxyinosine (U.S. Pat. No. 5,026,687 to Yarchoan et al.), benzimidazoles (U.S. Pat. No. 5,891,874 to Colacino et al.), plant extracts (U.S. Pat. No. 5,837,257 to Tsai et al., U.S. Pat. No. 5,725,859 to Omer et al., and U.S. Pat. No. 6,056,961), and piperidines (U.S. Pat. No. 5,830,905 to Diana et al.).

In certain embodiments, a compound of Formula I-VI or a composition comprising a compound of Formula I-VI is administered in combination or alternation with a second anti-viral agent selected from the group consisting of an interferon, a nucleotide analogue, a polymerase inhibitor, an NS3 protease inhibitor, an NS5A inhibitor, an entry inhibitor, a non-nucleoside polymerase inhibitor, a cyclosporine immune inhibitor, an NS4A antagonist, an NS4B-RNA binding inhibitor, a locked nucleic acid mRNA inhibitor, a cyclophilin inhibitor, and combinations thereof.

Exemplary Second Therapeutic Agents for Treatment of HCV

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with an anti-hepatitis C virus interferon, such as Intron A® (interferon alfa-2b) and; Roferon A® (Recombinant interferon alfa-2a), Infergen® (consensus interferon; interferon alfacon-1), PEG-Intron® (pegylated interferon alfa-2b), and Pegasys® (pegylated interferon alfa-2a). In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with ribavirin and in combination or alternation with an anti-hepatitis C virus interferon. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with ribavirin, in combination or alternation with an anti-hepatitis C virus interferon, and in combination or alternation with an anti-hepatitis C virus protease inhibitor. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with ribavirin. In certain embodiments, one or more compounds

provided herein can be administered in combination or alternation with an anti-hepatitis C virus interferon and without ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with an anti-hepatitis C virus interferon, in combination or alternation with an anti-hepatitis C virus protease inhibitor, and without ribavirin.

In certain embodiments, the anti-hepatitis C virus interferon is infergen, IL-29 (PEG-Interferon lambda), R7025 (Maxy-alpha), Belerofon, Oral Interferon alpha, BLX-883 (Locteron), omega interferon, multiferon, medusa interferon, Albuferon or REBIF®.

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with an anti-hepatitis C virus polymerase inhibitor, such as ribavirin, viramidine, HCV POL, NM 283 (valopicitabine), MK-0608, 7-Fluoro-MK-0608, PSI-6130, R1626, PSI-6206, PSI-938, R1479, HCV-796, VX-950 (Telaprevir, Vertex), GS 9190 NN (Gilead), GS 9256 (Gilead), PSI-7792 (BMS), BI 207127 (BI), R7128 (Roche), or PSI-7977 (Pharmasset), PSI-938 (Pharmasset), VX-222 (Vertex), ALS-2200 (Vertex), ALS-2158 (Vertex), MK-0608 (Merck), TMC649128 (Medivir), PF-868554 (Pfizer), PF-4878691 (Pfizer), ANA598 (Roche), VCH-759 (Vertex), IDX184 (Idenix), IDX375 (Idenix), A-837093 (Abbott), GS 9190 (Gilead), GSK625433 (GlaxoSmithKline), ABT-072 (Abbott), ABT-333 (Abbott), INX-189 (Inhibitex), or EDP-239 (Enanta).

In certain embodiments, the one or more compounds provided herein can be administered in combination with ribavarin and an anti-hepatitis C virus interferon, such as Intron A® (interferon alfa-2b) and Pegasys® (Peginterferon alfa-2a); Roferon A® (Recombinant interferon alfa-2a), Infergen® (consensus interferon; interferon alfacon-1), PEG-Intron® (pegylated interferon alfa-2b), Zalbin (albinterferon alfa-2b), omega interferon, pegylated interferon lambda, and Pegasys® (pegylated interferon alfa-2a).

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with an anti-hepatitis C virus protease inhibitor such as ITMN-191, SCH 503034 (bocepravir), VX950 (telaprevir), VX985, VX500, VX813, PHX1766, BMS-650032, GS 9256, BI 201335, IDX320, R7227, MK-7009 (vaniprevir), TMC435, BMS-791325, ACH-1625, ACH-2684, ABT-450, AVL-181, or Medivir HCV Protease Inhibitor.

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with an HCV NS5A inhibitor, such as BMS-790052 (daclatasvir, Bristol-Myers Squibb), PPI-461 (Presidio Pharmaceuticals), PPI-1301 (Presidio Pharmaceuticals), IDX-719 (Idenix Pharmaceuticals), AZD7295 (Arrow Therapeutics, AstraZeneca), EDP-239 (Enanta), ACH-2928 (Achillion), ACH-3102 (Achillion), ABT-267 (Abbott), or GS-5885 (Gilead).

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with an anti-hepatitis C virus vaccine, such as TG4040, PeviPROTM, CGI-5005, HCV/MF59, GV1001, IC41, GNI-103, GenPhar HCV vaccine, C-Vaxin, CSL123, Hepavaxx C, ChronVac-C® or INN00101 (E1).

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with an anti-hepatitis C virus monoclonal antibody, such as MBL-HCV1, AB68 or XTL-6865 (formerly HepX-C); or an anti-hepatitis C virus polyclonal antibody, such as cicavir.

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with an anti-hepatitis C virus immunomodulator, such as Zadaxin® (thymalfasin), SCV-07, NOV-205 or Oglufanide.

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with cyclophilin inhibitor, such as Enanta cyclophilin binder, SCY-635, or Debio-025.

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with Nexavar, doxorubicin, PI-88, amantadine, JBK-122, VGX-410C, MX-3253 (Ceglosivir), Suvus (BIVN-401 or virostat), PF-03491390 (formerly IDN-6556), G126270, UT-231B, DEBIO-025, EMZ702, ACH-0137171, MitoQ, ANA975, AVI-4065, Bavituxinab (Tarvacin), Alinia (nitrazoxanide) or PYN17.

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with telaprevir, bocepravir, interferon alfacon-1, interferon alfa-2b, pegylated interferon alpha 2a, pegylated interferon alpha 2b, ribavirin, or combinations thereof.

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with a protease inhibitor. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with telaprevir. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with bocepravir.

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with a protease inhibitor and in combination or alternation with ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with telaprevir and in combination or alternation with ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with bocepravir and in combination or alternation with ribavirin.

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with a protease inhibitor and not in combination or alternation with ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with telaprevir and not in combination or alternation with ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with bocepravir and not in combination or alternation with ribavirin.

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with an interferon. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with interferon alfacon-1. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with interferon alfa-2b. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with pegylated interferon alpha 2a. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with pegylated interferon alpha 2b.

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with an interferon and in combination or alternation with ribavirin.

In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with interferon alfacon-1 and in combination or alternation with ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with interferon alfa-2b and in combination or alternation with ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with pegylated interferon alpha 2a and in combination or alternation with ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with pegylated interferon alpha 2b and in combination or alternation with ribavirin.

In certain embodiments, one or more compounds can be administered in combination or alternation with one or more of the second agents provided herein and not in combination or alternation with ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with an interferon and not in combination or alternation with ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with interferon alfacon-1 and not in combination or alternation with ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with interferon alfa-2b and not in combination or alternation with ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with pegylated interferon alpha 2a and not in combination or alternation with ribavirin. In certain embodiments, one or more compounds provided herein can be administered in combination or alternation with pegylated interferon alpha 2b and not in combination or alternation with ribavirin.

EXAMPLES

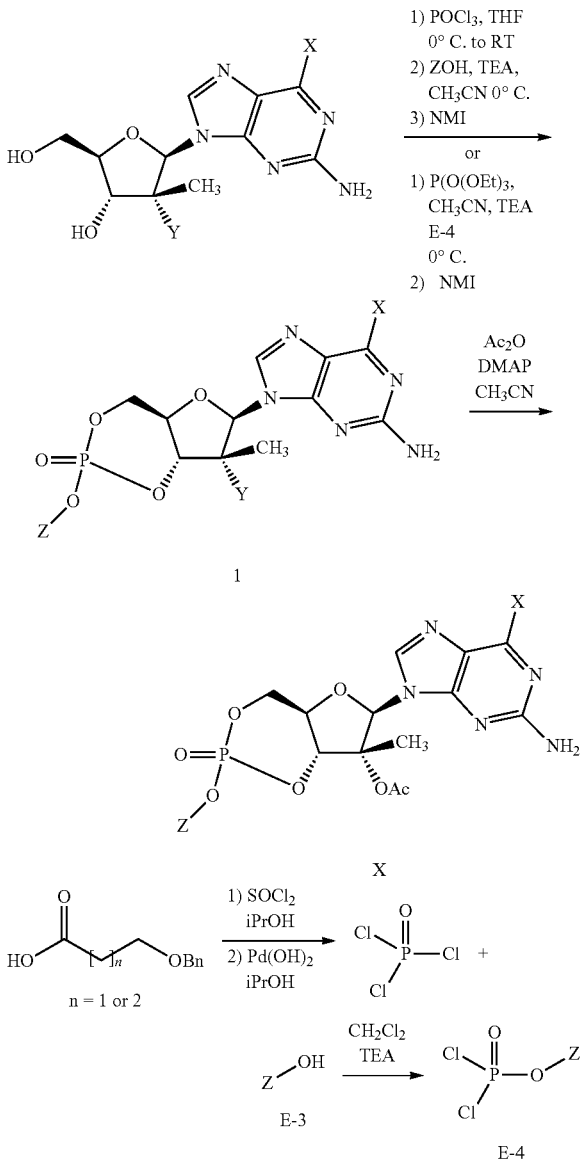
As used herein, the symbols and conventions used in these processes, schemes and examples, regardless of whether a particular abbreviation is specifically defined, are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Specifically, but without limitation, the following abbreviations may be used in the examples and throughout the specification: g (grams); mg (milligrams); mL (milliliters); μL (microliters); mM (millimolar); μM (micromolar); Hz (Hertz); MHz (megahertz); mmol (millimoles); hr or hrs (hours); min (minutes); MS (mass spectrometry); ESI (electrospray ionization); TLC (thin layer chromatography); HPLC (high pressure liquid chromatography); THF (tetrahydrofuran); $CDCl_3$ (deuterated chloroform); AcOH (acetic acid); DCM (dichloromethane); DMSO (dimethylsulfoxide); DMSO-d_6 (deuterated dimethylsulfoxide); EtOAc (ethyl acetate); MeOH (methanol); and BOC (t-butyloxycarbonyl).

For all of the following examples, standard work-up and purification methods known to those skilled in the art can be utilized. Unless otherwise indicated, all temperatures are expressed in ° C. (degrees Centigrade). All reactions are conducted at room temperature unless otherwise noted. Synthetic methodologies illustrated herein are intended to exemplify the applicable chemistry through the use of specific examples and are not indicative of the scope of the disclosure.

Example 1

Synthesis of 3',5'-Cyclic Phosphate Compounds

Scheme 2



Compounds provided in Scheme 2 are as described below:

28: X═OMe, Z=iPrOC(O)CH_2— and Y═OH

29: X═OMe, Z=EtOC(O)$(CH_2)_3$— and Y═OH

31: X═OMe, Z=(R)-EtOC(O)$CH_2CH(CH_3)$— and Y═OH

27: X═OMe, Z=$PhCH_2OC(O)CH_2$— and Y═OH

37: X═OMe, Z=$HO(CH_2)_2S$—$S(CH_2)_2$— and Y═OH

26: X═OMe, Z=iPrOC(O)CH_2— and Y═F

24: X═OEt, Z=tBuS-$S(CH_2)_2$— and Y═F

22: X═OEt, Z=iPrOC(O)$(CH_2)_2$— and Y═OH

30: X═OMe, Z=(R)-EtOC(O)$CH(CH_3)$— and Y═OH

32: X═OMe, Z=iPrOC(O)CH_2— and Y═OAc

E-3a: Z=iPrOC(O)$(CH_2)_2$—

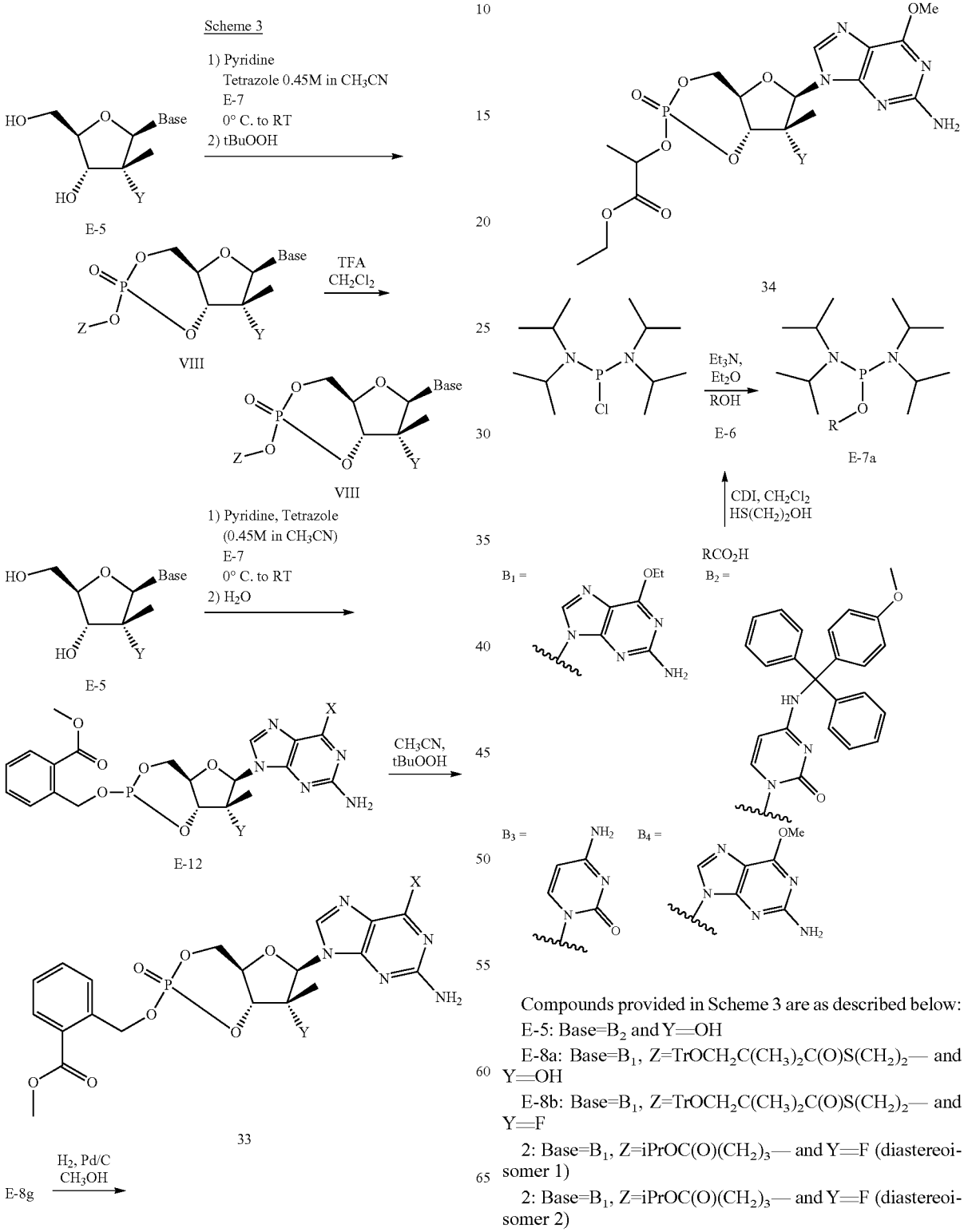
E-3b: Z=iPrOC(O)$(CH_2)_3$—

E-4-a: Z=tBuS-S$(CH_2)_2$—

E-4-b: Z=iPrOC(O)$(CH_2)_2$—

E-4-c: Z=(R)-EtOC(O)CH(CH_3)—

Scheme 3



Compounds provided in Scheme 3 are as described below:

E-5: Base=B_2 and Y═OH

E-8a: Base=B_1, Z=TrO$CH_2C(CH_3)_2C(O)S(CH_2)_2$— and Y═OH

E-8b: Base=B_1, Z=TrO$CH_2C(CH_3)_2C(O)S(CH_2)_2$— and Y═F

2: Base=B_1, Z=iPrOC(O)$(CH_2)_3$— and Y═F (diastereoisomer 1)

2: Base=B_1, Z=iPrOC(O)$(CH_2)_3$— and Y═F (diastereoisomer 2)

E-8e: Base=B_2, Z=$EtOC(O)NHCH_2C(CH_3)_2C(O)S(CH_2)_2$— and Y═OH

E-8f: Base=B_2, Z=$EtOC(O)C(CH_3)_2C(O)S(CH_2)_2$— and Y═OH

E-8g: Base=B_4, Z=$PhCH_2$— and Y═OH

1: Base=B_1, Z=$iPrOC(O)(CH_2)_3$— and Y═OH (diastereoisomer 1)

1: Base=B_1, Z=$iPrOC(O)(CH_2)_3$— and Y═OH (diastereoisomer 2)

4: Base=B_1, Z=$HOCH_2C(CH_3)_2C(O)S(CH_2)_2$— and Y═OH (diastereoisomer 1)

4: Base=B_1, Z=$HOCH_2C(CH_3)_2C(O)S(CH_2)_2$— and Y═OH (diastereoisomer 2)

5: Base=B_1, Z=$HOCH_2C(CH_3)_2C(O)S(CH_2)_2$— and Y═F (diastereoisomer 1)

5: Base=B_1, Z=$HOCH_2C(CH_3)_2C(O)S(CH_2)_2$— and Y═F (diastereoisomer 2)

67: Base=B_3, Z=$EtOC(O)NHCH_2C(CH_3)_2C(O)S(CH_2)_2$— and Y═OH

66: Base=B_3, Z=$EtOC(O)C(CH_3)_2C(O)S(CH_2)_2$— and Y═OH

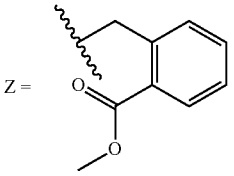
E-7a: Z=$TrOCH_2C(CH_3)_2C(O)S(CH_2)_2$—

E-7b: Z=$iPrOC(O)(CH_2)_3$—

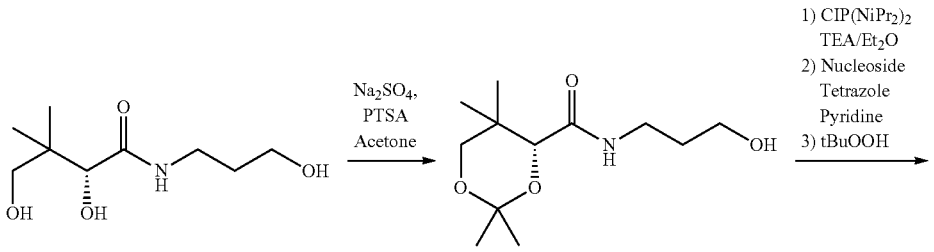
E-7c: Z=$EtOC(O)NHCH_2C(CH_3)_2C(O)S(CH_2)_2$—

E-7d: Z=$EtOC(O)C(CH_3)_2C(O)S(CH_2)_2$—

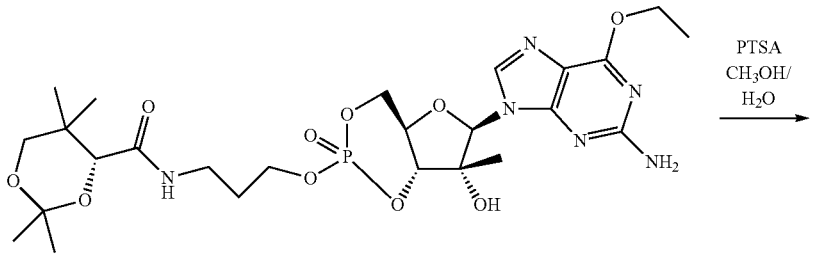
E-7e:



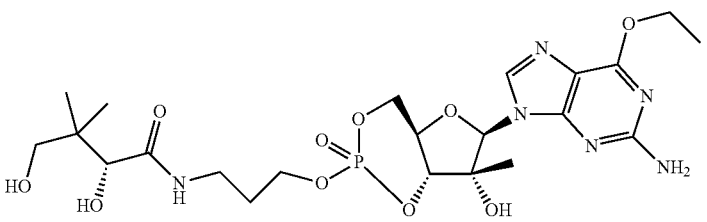
Scheme 4



E-14



38



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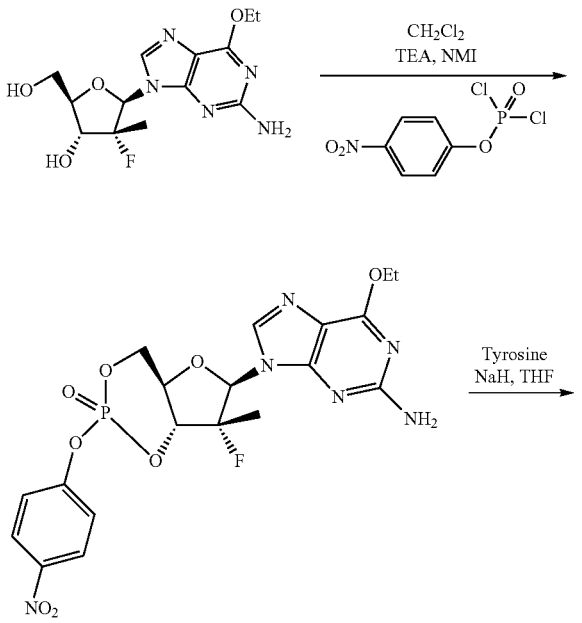
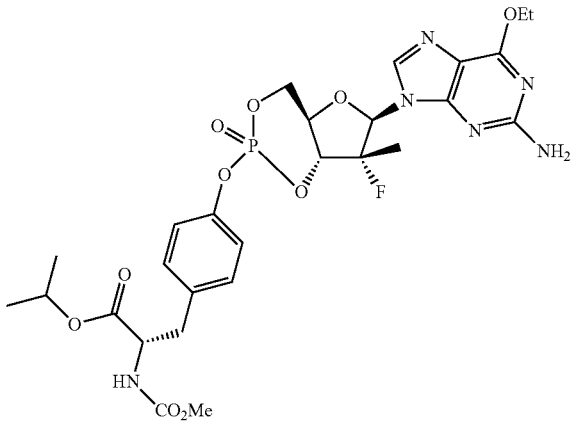
Scheme 5



E-17



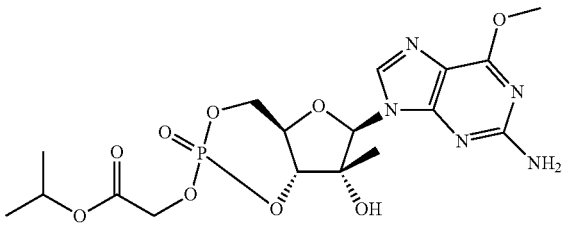
13

General Method A.

The following procedure was used to obtain compounds 28, 29, 31, 27, 37, and 26.

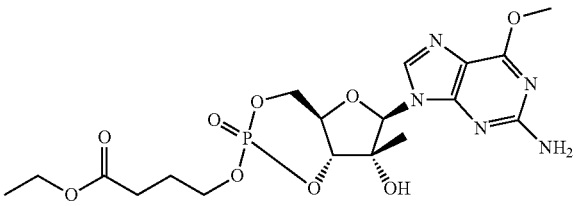
The nucleoside (3.21 mmol) was suspended in THF (25 ml). Under nitrogen and at 0° C., $POCl_3$ (4.82 mmol) was added and the reaction mixture was allowed to reach at room temperature overnight. The reaction mixture was cooled down to 0° C. and a mixture of alcohol (3.53 mmol) and TEA (16.06 mmol) in CH_3CN (10 ml) was added dropwise. The mixture was stirred at 0° C. during 1 hour. N-Methylimidazole (19.27 mmol) was added at 0° C. and after 15 min at 0° C., the reaction mixture was stirred at room temperature during 2 hours. The mixture was quenched on a solution 0.5M phosphate buffer (pH=7) and the product was extracted with CH_2Cl_2. The organic layer was dried on Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography (eluent: CH_2Cl_2/CH_3CH_2OH 0 to 20%) and by preparative MS/HPLC to give the expected compounds as a mixture of diastereoisomers.

28



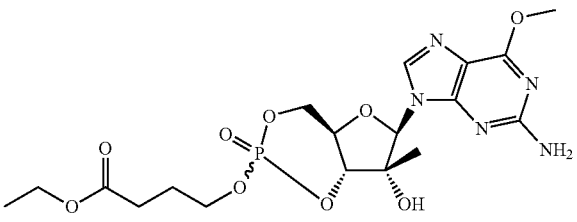
White solid; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm) 0.95 (s, 3H), 1.21-1.23 (m, 6H), 3.95 (s, 3H), 4.22-4.29 (m, 0.7H), 4.46-4.53 (m, 0.3H), 4.63-4.75 (m, 4H), 4.96-5.03 (m, 1H), 5.93 (brs, 1H), 6.07 (brs, 0.3H), 6.14 (brs, 0.7H), 6.48 (brs, 1H), 6.59 (s, 1H), 8.05 (s, 0.7H), 8.12 (brs, 0.3H); ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −5.84 (s, 0.68P), −5.01 (s, 0.32P); MS (ESI) m/z=474.2 (MH^+).

29



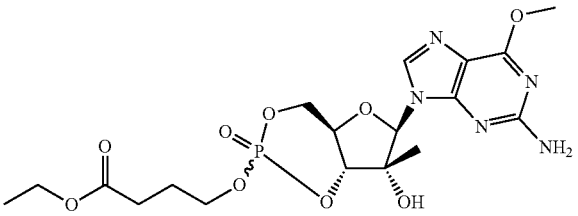
White solid; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm) 0.92 (s, 2.1H), 0.94 (s, 0.9H), 1.14 (t, J=7.10 Hz, 2.1H), 1.18 (t, J=7.10 Hz, 0.9H), 1.86-1.98 (m, 2H), 2.38-2.48 (m, 2H), 3.95 (s, 3H), 4.00-4.13 (m, 4.3H), 4.19-4.25 (m, 0.7H), 4.59-4.66 (m, 2H), 5.93 (s, 1H), 6.13 (brs, 1H), 6.51 (brs, 1H), 6.57 (s, 1H), 8.12 (brs, 1H); ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −5.86 (s, 0.70P), −4.77 (s, 0.30P); MS (ESI) m/z=488.2 (MH^+).

In this case, the mixture was purified by chiral chromatography to give the 2 pure diastereoisomers.



Diastereoisomer 1

-continued



Diastereoisomer 2

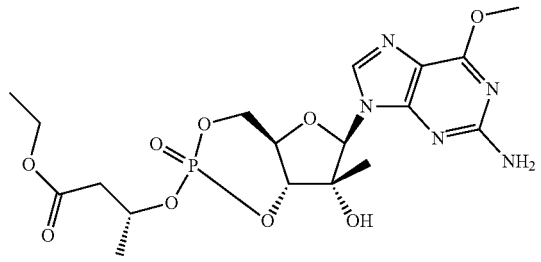
(29): Diastereoisomer 1

White solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 0.94 (s, 3H), 1.19 (t, J=7.10 Hz, 3H), 1.89 (quintuplet, J=6.76 Hz, 2H), 2.40 (t, J=7.38 Hz, 2H), 3.95 (s, 3H), 4.04-4.11 (m, 4H), 4.36-4.42 (m, 1H), 4.62-4.67 (m, 2H), 5.93 (s, 1H), 6.04 (brs, 1H), 6.57 (brs, 2H), 8.13 (brs, 1H); ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −4.76 (s, 1P); MS (ESI) m/z=488.2 (MH^+).

(29): Diastereoisomer 2:

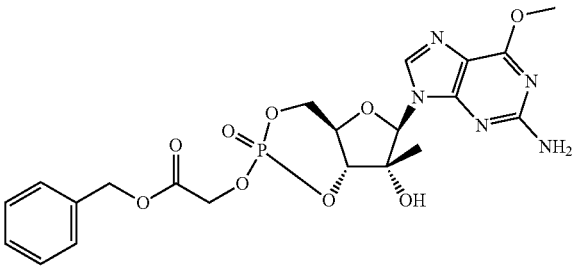
White solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 0.93 (s, 3H), 1.14 (t, J=7.09 Hz, 3H), 1.89 (quintuplet, J=6.84 Hz, 2H), 2.45 (t, J=7.21 Hz, 2H), 3.95 (s, 3H), 4.02 (q, J=7.05 Hz, 2H), 4.08-4.13 (m, 2H), 4.19-4.25 (m, 1H), 4.58-4.67 (m, 2H), 5.94 (s, 1H), 6.13 (s, 1H), 6.51 (brs, 2H), 8.12 (brs, 1H); ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −5.87 (s, 1P); MS (ESI) m/z=488.2 (MH^+).

31



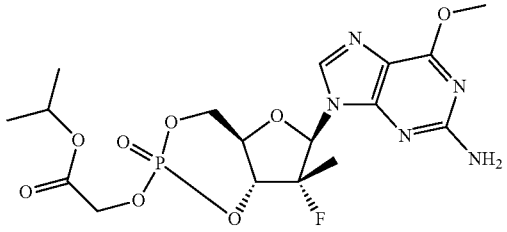
For this compound, the alcohol was added at room temperature and the reaction was made without NMI. White solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 0.94-0.95 (m, 3H), 1.14-1.22 (m, 3H), 1.36 (d, J=6.22 Hz, 0.6H), 1.42 (d, J=6.22 Hz, 2.40H), 2.68-2.75 (m, 2H), 3.95 (s, 3H), 4-4.12 (m, 2H), 4.19-4.25 (m, 1H), 4.53-4.66 (m, 2H), 4.74-4.82 (m, 1H), 5.93 (s, 1H), 6.13 (s, 1H), 6.50-6.57 (m, 2H), 8.05 (brs, 0.8H), 8.12 (brs, 0.2H); ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −7.75 (s, 0.80P), −5.32 (s, 0.20P); MS (ESI) m/z=488.2 (MH^+)

27



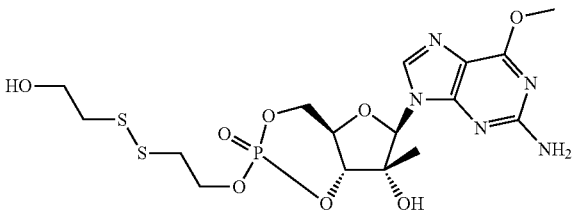
The procedure was the same as that described for compound 1c. White solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 0.93 (s, 2H), 0.94 (s, 1H), 3.95 (s, 1H), 3.96 (s, 2H), 4.22-4.28 (m, 0.67H), 4.44-4.51 (m, 0.33H), 4.61-4.69 (m, 2H), 4.77-4.86 (m, 2H), 5.21 (s, 2H), 5.93 (brs, 1H), 6.07 (brs, 0.33H), 6.13 (s, 0.67H), 6.49 (brs, 1H), 6.59 (s, 1H), 7.31-7.42 (m, 5H), 8.05 (s, 0.67H), 8.12 (brs, 0.33H); ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −5.94 (s, 0.67P), −5.02 (s, 0.33P); MS (ESI) m/z=522.2 (MH^+).

26



For this reaction, the solvent was $P(OEt)_3$. White solid; 4% yield; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 1.21-1.27 (m, 9H), 3.95-3.96 (m, 3H), 4.24-4.30 (m, 1H), 4.64-4.78 (m, 4H), 5.00 (septuplet, J=6.22 Hz, 1H), 6.26-6.33 (m, 1H), 6.52 (brs, 2H), 8.10 (brs, 1H); ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −6.51 (s, 0.90P), −5.21 (s, 0.10P); ^{19}F NMR (DMSO-d_6, 376.50 MHz) δ (ppm) −158.57 (1F); MS (ESI) m/z=476.2 (MH^+).

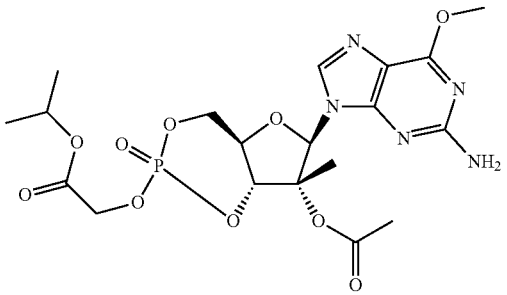
37



(2R,3R,4R,5R)-2-(2-amino-6-methoxy-purin-9-yl)-5-(hydroxymethyl)-3-methyl-tetrahydrofuran-3,4-diol (1.606

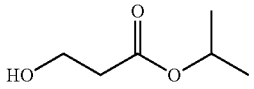
mmol) was suspended in THF (15 ml). Under nitrogen and at 0° C., $POCl_3$ (2.40 mmol) was added and the reaction mixture was allowed to reach room temperature overnight. Under nitrogen and at 0° C., tBuMgCl (7.23 mmol) was added dropwise to a solution of 2-hydroxyethyl disulfide (2.40 mmol) in THF (5 mL). The reaction mixture was stirred at 0° C. during 30 minutes. At room temperature and under nitrogen, TEA (8.03 mmol) was added to the first solution followed by dropwise addition of the second solution at 0° C. The reaction mixture was stirred at 0° C. during 30 minutes and was allowed to reach room temperature overnight. The mixture was quenched with a 0.5M solution of phosphate buffer (pH=7) and the product was extracted with CH_2Cl_2. The organic layer was dried on Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography (eluent: CH_2Cl_2/CH_3CH_2OH 0 to 10%) and by preparative MS/HPLC to give the expected compounds as a white solid. ^1H NMR (MeOD, 400 MHz) δ (ppm) 0.98 (s, 2.1H), 1.14 (s, 0.9), 2.88 (t, J=6.37 Hz, 0.7H), 2.94-3.03 (m, 2.6H), 3.07 (t, J=6.60 Hz, 0.7H), 3.80 (t, J=6.37 Hz, 1H), 4.05 (s, 0.9H), 4.06 (s, 2.1H), 4.18-4.22 (m, 2H), 4.27-4.30 (m, 1H), 4.40-4.57 (m, 4H), 4.66-4.78 (m, 1H), 5.96 (brs, 0.3H), 5.97 (s, 0.7H), 7.94 (s, 0.3H), 7.95 (s, 0.7H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −3.40 (s, 0.3P), −1.94 (s, 0.7P); MS (ESI) m/z=510.2 (MH^+).

32



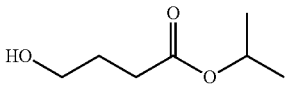
Compound Ia (0.04 mmol) was suspended in CH_3CN (0.250 ml). Under nitrogen and at 0° C., Ac_2O (0.12 mmol), TEA (0.24 mmol) and DMAP (0.004 mmol) were added and the reaction mixture was stirred at room temperature during 2 hours. AcOEt was added and the mixture was washed with H_2O. The organic layer was dried on Na_2SO_4, filtered and concentrated. The crude was purified by preparative MS/HPLC to give the expected compound as a white solid in 64% yield. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm) 1.22-1.24 (m, 6H), 1.37 (s, 2.1H), 1.39 (s, 0.9H), 2.11 (s, 0.9H), 2.14 (s, 2.1H), 3.95 (s, 0.9H), 3.96 (s, 2.1H), 4.21-4.27 (m, 0.7H), 4.49-4.58 (m, 1.3H), 4.67-4.79 (m, 3H), 4.97-5.04 (m, 1H), 5.43 (brs, 1H), 6.40 (brs, 1H), 6.48 (s, 0.3H), 6.50 (s, 0.7H), 6.63 (brs, 1H), 7.90 (brs, 1H); ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −6.48 (s, 0.70P), −5.80 (s, 0.30P); MS (ESI) m/z=516.2 (MH^+).

Isopropyl 3-hydroxypropanoate (E-3a)



To a solution of 3-benzyloxypropanoic acid (27.7 mmol) in propan-2-ol (40 mL) under nitrogen at 0° C. was added dropwise thionyl chloride (30.5 mmol). The reaction mixture was allowed to reach room temperature over 30 minutes and stirred at room temperature overnight. The mixture was diluted with CH_2Cl_2 and washed with a saturated solution of $NaHCO_3$ and brine. The organic layer was dried on Na_2SO_4, filtered and concentrated under reduced pressure. The crude was diluted with isopropanol (80 mL) and $Pd(OH)_2$ (20%, 1 g) in isopropanol was added. The system (reaction in a stainless steel reactor) was purged with nitrogen, vacuum and H_2 and the reaction mixture was stirred under H_2 atmosphere (3 bars) overnight at room temperature. The reaction mixture was filtered through autocup and the precipitate was washed with isopropanol. The filtrates were concentrated under reduced pressure and dried under vacuum pump to give the expected compound in 78% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.26 (d, J=6.31 Hz, 6H), 2.19 (brs, 1H), 2.54 (t, J=5.56 Hz, 2H), 3.86 (t, J=5.56 Hz, 2H), 5.06 (heptuplet, J=6.25 Hz, 1H).

Isopropyl 4-hydroxybutanoate (E-3b)



To a solution of 4-benzyloxybutyric acid (20.59 mmol) in propan-2-ol (30 mL) under nitrogen at 0° C. was added dropwise thionyl chloride (22.65 mmol). The reaction mixture was allowed to reach room temperature over 30 minutes and stirred at room temperature during 20 hours. The mixture was concentrated under reduced pressure and co-evaporated with CH_2Cl_2. The crude was dried under vacuum pump to give the expected compound as yellow oil in quantitative yield. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.22 (d, J=6.26 Hz, 6H), 1.94 (quintuplet, J=6.70 Hz, 2H), 2.40 (t, J=7.47 Hz, 2H), 3.50-3.53 (m, 2H), 4.51 (s, 2H), 5 (heptuplet, J=6.22 Hz, 1H), 7.28-7.38 (m, 5H); MS (ESI) m/z=259.6 (MNa^+).

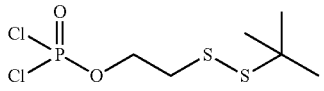
The previous compound (12.10 mmol) in isopropanol (30 mL) was added to $Pd(OH)_2$ (20%, 0.572 mg) in isopropanol (10 mL). The system was purged with nitrogen, vacuum and H_2 and the reaction mixture was stirred under H_2 atmosphere overnight at room temperature. The reaction mixture was filtered through autocup (nylon 0.45 μM) and the precipitate was washed with isopropanol. The filtrates were concentrated under reduced pressure and dried under vacuum pump to give the expected compound as a translucent liquid in 75% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.24 (d, J=6.27 Hz, 6H), 1.88 (quintuplet, J=6.61 Hz, 2H), 2.41 (t, J=7.09 Hz, 2H), 3.70 (t, J=6.12 Hz, 2H), 5.02 (heptuplet, J=6.35 Hz, 1H).

General Method B.

The following procedure was used to obtain compounds E-4-a, E-4-b, and E-4-c.

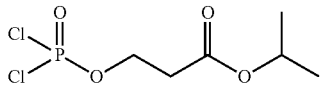
To a solution of $P(O)Cl_3$ (1.44 mmol) in CH_2Cl_2 (5 mL) was added at −15° C. under nitrogen a solution of appropriate alcohol (1.313 mmol) and TEA (1.313 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at ~(−15° C.) during 1 hour. The solvent was evaporated under reduced pressure. Et_2O (10 mL) was added and the salts were filtered-off before concentration of the filtrate to give the expected compound.

2-(2-dichlorophosphoryloxyethyldisulfanyl)-2-methyl-propane (E-4-a)



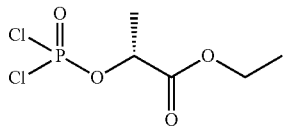
The crude was used for the next step without being analyzed.

Isopropyl 3-dichlorophosphoryloxypropanoate (E-4-b)



^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm) 6.78 (s, 1P).

Ethyl (2R)-2-dichlorophosphoryloxypropanoate (E-4-c)



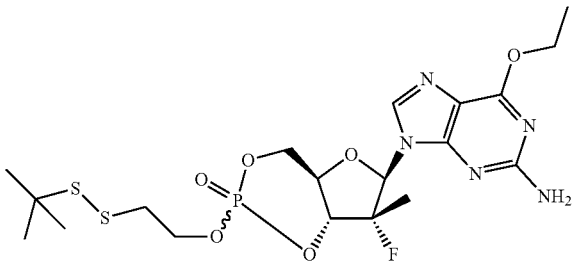
The expected compound was obtained as impure material. Yellow translucent oil; ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm) 8.41 (s, 1P).

General Method C.

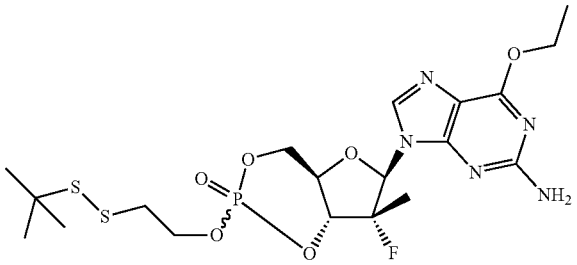
The following procedure was used to obtain compounds 24, 22 and 30.

Under nitrogen, the nucleoside (0.482 mmol) was partially dissolved in a solution of CH_3CN (1.5 mL), $P(O)(OEt)_3$ (1.5 mL) and TEA (1.93 mmol). The reaction mixture was cooled down to 0° C. Compound E-4 (0.626 mmol) was added and after 30 minutes of stirring, NMI (1.01 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight. The reaction was diluted with EtOAc (or CH_2Cl_2) and washed with H_2O (or brine). The aqueous phase was extracted with EtOAc (or CH_2Cl_2) and the combined organic layers were dried on Na_2SO_4, filtered and concentrated. The crude was purified by chromatography on a silica gel column (eluent: CH_2Cl_2/CH_3CH_2OH 0 to 5%) and by preparative MS/HPLC to give the pure expected compounds or as a mixture of diastereoisomers.

24



Diastereoisomer 1



Diastereoisomer 2

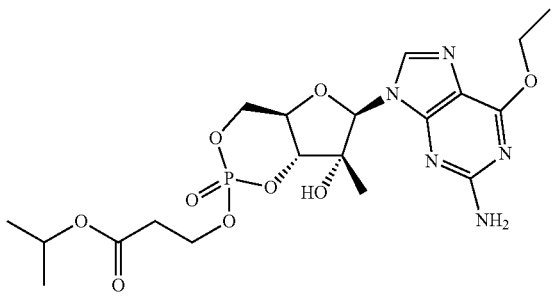
(24): Diastereoisomer 1:

White solid; ^1H NMR (MeOD, 400 MHz) δ (ppm) 1.33 (d, J=22.54 Hz, 3H), 1.34 (s, 9H), 1.44 (t, J=7.08 Hz, 3H), 3.10 (t, J=6.20 Hz, 2H), 4.36-4.47 (m, 3H), 4.55 (q, J=7.06 Hz, 2H), 4.69-4.79 (m, 2H), 5.41 (brs, 1H), 6.30 (d, J=19.69 Hz, 1H), 7.97 (s, 1H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −5.86 (s, 1P); ^{19}F NMR (MeOD, δ76.5 MHz) δ (ppm) −161.48 (1F); MS (ESI) m/z=538.0 (MH^+).

(24): Diastereoisomer 2:

White solid; ^1H NMR (MeOD, 400 MHz) δ (ppm) 1.26 (s, 9H), 1.29 (d, J=22.42 Hz, 3H), 1.33 (t, J=7.11 Hz, 3H), 2.92 (t, J=6.60 Hz, 2H), 4.27-4.32 (m, 2H), 4.39-4.46 (m, 3H), 4.53-4.60 (m, 1H), 4.64-4.71 (m, 1H), 5.65 (brs, 1H), 6.16 (d, J=20.61 Hz, 1H), 7.85 (s, 1H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −3.79 (s, 1P); ^{19}F NMR (MeOD, δ76.5 MHz) δ (ppm) −160.44 (1F); MS (ESI) m/z=538.0 (MH^+).

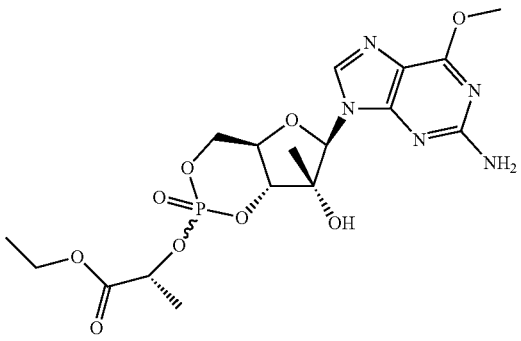
22



White solid; ^1H NMR (MeOD, 400 MHz) δ (ppm) 1.12 (s, 2.2H), 1.14 (s, 0.8H), 1.25-1.29 (m, 6H), 1.42-1.47 (m, 3H),

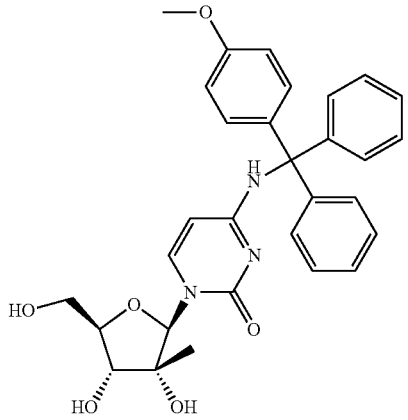
2.74-2.83 (m, 2H), 4.40-4.44 (m, 3H), 4.52-4.58 (m, 2H), 4.61-4.73 (m, 2H), 5.05-5.13 (m, 2H), 5.97 (s, 0.27H), 6.02 (s, 0.73H), 7.93 (s, 0.27H), 7.95 (s, 0.73H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −5.49 (s, 0.73P), −3.55 (s, 0.27P); MS (ESI) m/z=502.2 (MH^+).

30



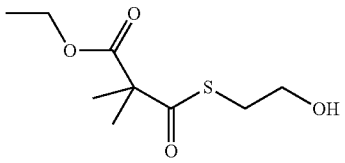
White solid; ^{1}H NMR (MeOD, 400 MHz) δ (ppm) 1.11 (s, 3H), 1.27 (t, J=7.02 Hz, 3H), 1.65 (d, J=6.87 Hz, 3H), 4.06 (s, 3H), 4.20-4.26 (m, 2H), 4.37-4.43 (m, 1H), 4.66-4.76 (m, 2H), 4.98-5.06 (m, 1H), 5.39 (brs, 1H), 5.98 (s, 1H), 7.96 (s, 1H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −6.19 (s, 1P); MS (ESI) m/z=474.2 (MH^+).

1-[(2R,3R,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)-3-methyl-tetrahydrofuran-2-yl]-4-[[(4-methoxyphenyl)-diphenyl-methyl]amino]pyrimidin-2-one (E-5)



2'-C-Methylcytidine (38.9 mmol) was dissolved in pyridine (270 mL) and the reaction mixture was cooled down to 0° C. TMSCl (233.4 mmol) was added and the mixture was stirred at room temperature during 4 hours. DMAP (38.9 mmol) and mMTrCl (77.25 mmol) were added and the reaction mixture was stirred at 50° C. during 2 days. The reaction was cooled down to room temperature and a saturated solution of $NaHCO_3$ was added slowly. The mixture was extracted with CH_2Cl_2 and the organic layer was dried over Na_2SO_4, filtered and concentrated. Co-evaporations with toluene and CH_2Cl_2 were done. The crude was dissolved in CH_3OH (500 mL) and NH_4F (194.5 mmol) was added. The reaction mixture was heated at reflux and stirred during 1 hour. The reaction mixture was cooled down to room temperature and concentrated. The crude was purified by chromatography on a silica gel column (eluent: CH_2Cl_2/CH_3OH 0 to 10%) to give the expected compound as a yellow powder in 89% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.08 (s, 3H), 3.71-3.84 (m, 2H), 3.81 (s, 3H), 3.90-3.94 (m, 1H), 3.99-4.03 (m, 1H), 5.14 (d, J=7.63 Hz, 1H), 5.31 (s, 1H), 5.79 (brs, 1H), 6.84 (d, J=8.65 Hz, 2H), 7.13 (d, J=8.69 Hz, 2H), 7.21 (d, J=7.35 Hz, 4H), 7.27-7.34 (m, 8H), 7.51 (brs, 1H).

Ethyl 3-(2-hydroxyethylsulfanyl)-2,2-dimethyl-3-oxo-propanoate (E-6)



To a solution of 3-ethoxy-2,2-dimethyl-3-oxopropionic acid (30.78 mmol) in anhydrous CH_2Cl_2 (20 mL) was added portionwise CDI (40.02 mmol). The reaction mixture was stirred at room temperature during 30 minutes. This solution was added dropwise at −40° C.<T<−30° C. to a solution of 2-mercaptoethanol (41.21 mmol) in anhydrous CH_2Cl_2 (60 mL). The mixture was stirred at −40° C.<T<−30° C. during 2 hours. The reaction mixture was washed with ice-cold water (×3), dried through a phase separator and evaporated in vacuo while keeping the crude mixture below 25° C. The crude was purified by chromatography on a silica gel column (eluent: petroleum ether/EtOAc 95/5 to 50/50) to give the expected compound as a colorless oil in 30% yield. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 1.15 (t, J=7.05 Hz, 3H), 1.38 (s, 6H), 2.94 (t, J=6.59 Hz, 2H), 3.43-3.48 (m, 2H), 4.10 (q, J=7.04 Hz, 2H), 4.96 (t, J=5.44 Hz, 1H); MS (ESI) m/z=243 (MNa^+).

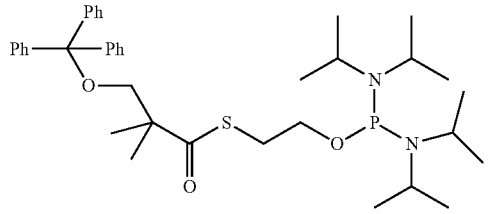
General Method C.

The following procedure was used to obtain intermediates E-7a, E-7b, E-7c, E-7d, and E-7e.

To a solution of 2-bis(diisopropylamino)chlorophosphine (4.25 mmol) in anhydrous diethyl ether (5 mL/mmol) (3 times vacuo/nitrogen) under nitrogen was added at −15° C. triethylamine (12.70 mmol) followed by a solution of an appropriate alcohol (5.08 mmol) in anhydrous ether (2.5 mL/mmol). The reaction mixture was stirred at −15° C. for 1.5 hours then allowed to warm up to room temperature, and stirred at room temperature for 3.5 hours. The reaction mixture was filtered through an autocup (0.45 μm) to remove salts and washed

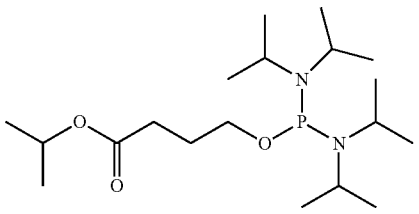
with diethyl ether. The filtrate was evaporated under reduced pressure under nitrogen to give the expected intermediate.

S-[2-bis(diisopropylamino)phosphanyloxyethyl]-2,2-dimethyl-3-trityloxy-propanethioate (E-7a)



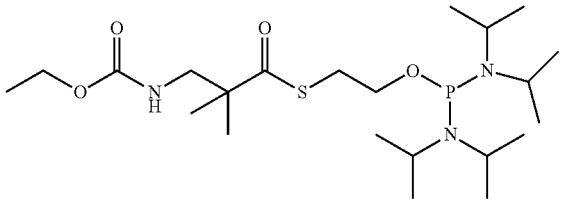
Quantitative yield; ^{31}P NMR ($CDCl_3$, 161.98 MHz) δ (ppm) 124.79 (s, 1P).

Isopropyl 4-bis(diisopropylamino)phosphanyloxybutanoate (E-7b)



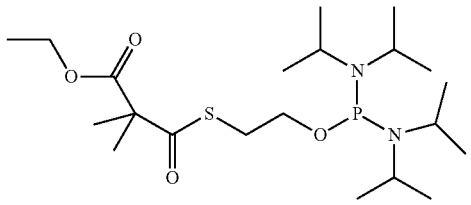
Yellow colorless oil; Quantitative yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.15 (d, J=4.58 Hz, 12H), 1.16 (d, J=4.44 Hz, 12H), 1.22 (d, J=6.25 Hz, 6H), 1.86-1.93 (m, 2H), 2.40 (t, J=7.42 Hz, 2H), 2.48-2.58 (m, 2H), 3.45-3.60 (m, 4H), 5.00 (heptuplet, J=6.05 Hz, 1H); ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm) 123.87 (s, 1P).

S-[2-bis(diisopropylamino)phosphanyloxyethyl]-3-(ethoxycarbonylamino)-2,2-dimethyl-propanethioate (E-7c)



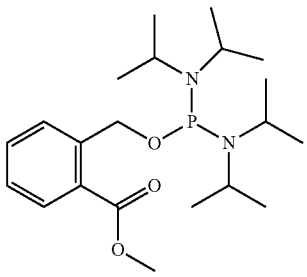
Yellow oil; quantitative yield; ^{31}P NMR ($CDCl_3$, 161.98 MHz) δ (ppm) 124.62 (s, 1P).

Ethyl 3-[2-bis(diisopropylamino)phosphanyloxyethylsulfanyl]-2,2-dimethyl-3-oxo-propanoate (E-7d)



Yellowish oil; Quantitative yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.08 (d, J=4.60 Hz, 12H), 1.09 (d, J=4.60 Hz, 12H), 1.14-1.25 (m, 5H), 1.41 (s, 6H), 3.07 (t, J=6.33 Hz, 2H), 3.37-3.52 (m, 4H), 4.11 (q, J=7.10 Hz, 2H); ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm) 124.63 (s, 1P).

Methyl 2-[bis(diisopropylamino)phosphanyloxymethyl]benzoate (E-7e)



^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) 119.82 (s, 1P).

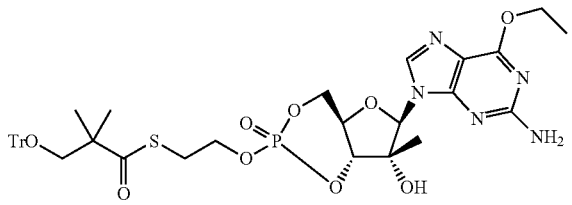
General Procedure D:

The following procedure was used to obtain compounds E-8a, E-8b, 20, E-8e, E-8f, and 1.

To a solution of nucleoside (2.94 mmol) and tetrazole (0.45M in CH_3CN)(6.5 mL/mmol) in pyridine (15 mL) was added the compound E-7 (4.44 mmol) in pyridine (5 mL) at 0° C. under nitrogen. The reaction mixture was stirred at room temperature overnight. tBuOOH (6M in decane)(0.5 mL/mmol) was added and the reaction mixture was stirred at room temperature. The reaction mixture was concentrated under reduced pressure. The crude was dissolved in EtOAc an washed with a solution of HCl 1N, a saturated solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude was purified by chromatography on a silica gel column (eluent: CH_2Cl_2/

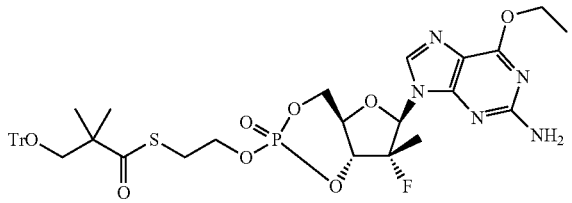
CH_3OH 0 to 10%) (and by preparative MS/HPLC if necessary) to give the expected compound.

E-8a



MS (ESI) m/z=790.21 (MH^+).

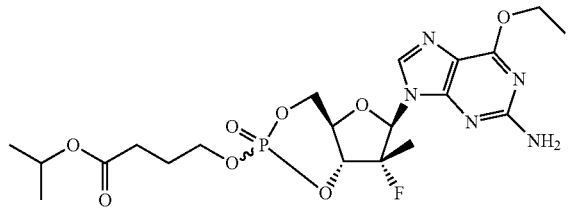
E-8b



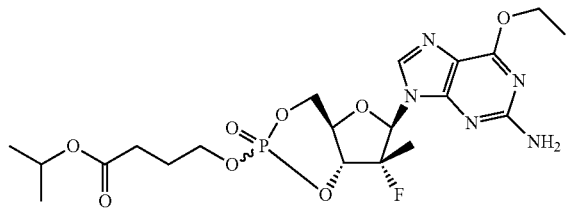
The expected compound was not isolated as pure material and was used as is for the next step.

MS (ESI) m/z=792.4 (MH^+).

20



Diastereoisomer 1



Diastereoisomer 2

In this case, work-up was skipped. The reaction mixture was concentrated under reduced pressure and co-evaporated with toluene before purification by chromatography and preparative MS/HPLC to give the 2 pure diastereoisomers.

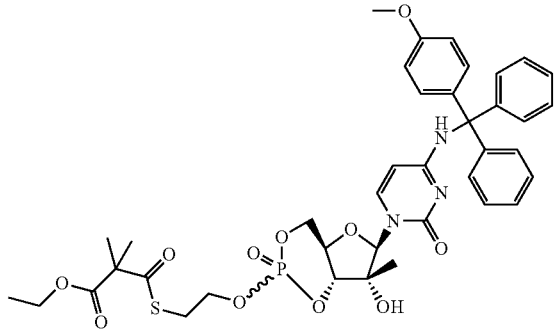
(20): Diastereoisomer 1:

White solid; 12% yield; ^1H NMR (MeOD, 400 MHz) δ (ppm) 1.25 (d, J=6.27 Hz, 6H), 1.39 (d, J=23.18 Hz, 3H), 1.44 (t, J=7.07 Hz, 3H), 2.04 (quintuplet, J=6.62 Hz, 2H), 2.45 (t, J=7.09 Hz, 2H), 4.24-4.29 (m, 2H), 4.43-4.50 (m, 1H), 4.54 (q, J=7.08 Hz, 2H), 4.63-4.70 (m, 1H), 4.72-4.80 (m, 1H), 5 (septuplet, J=6.30 Hz, 1H), 5.76 (brs, 1H), 6.26 (d, J=20.65 Hz, 1H), 7.95 (s, 1H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −3.58 (s, 1P); ^{19}F NMR (MeOD, δ76.5 MHz) δ (ppm) −160.70 (1F); MS (ESI) m/z=518.07 (MH^+).

(20): Diastereoisomer 2:

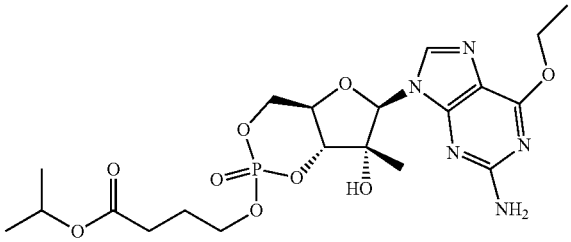
White solid; 11% yield; ^1H NMR (MeOD, 400 MHz) δ (ppm) 1.21 (d, J=6.22 Hz, 6H), 1.32 (d, J=22.36 Hz, 3H), 1.44 (t, J=7.11 Hz, 3H), 2.11 (quintuplet, J=6.45 Hz, 2H), 2.50 (t, J=7.02 Hz, 2H), 4.25-4.30 (m, 2H), 4.34-4.40 (m, 1H), 4.54 (q, J=7.11 Hz, 2H), 4.69-4.78 (m, 2H), 4.97 (septuplet, J=6.27 Hz, 1H), 5.36 (brs, 1H), 6.30 (d, J=20.09 Hz, 1H), 8.01 (s, 1H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −5.58 (s, 1P); ^{19}F NMR (MeOD, δ76.5 MHz) δ (ppm) −161.43 (1F); MS (ESI) m/z=518.07 (MH^+).

E-8f



In this case, pure diastereoisomer was isolated after chromatography. White solid; 15% yield. MS (ESI) m/z=792.2 (MH^+).

1



In this case, the mixture was purified by chiral HPLC to give the 2 pure diastereoisomers.

(1): Diastereoisomer 1:

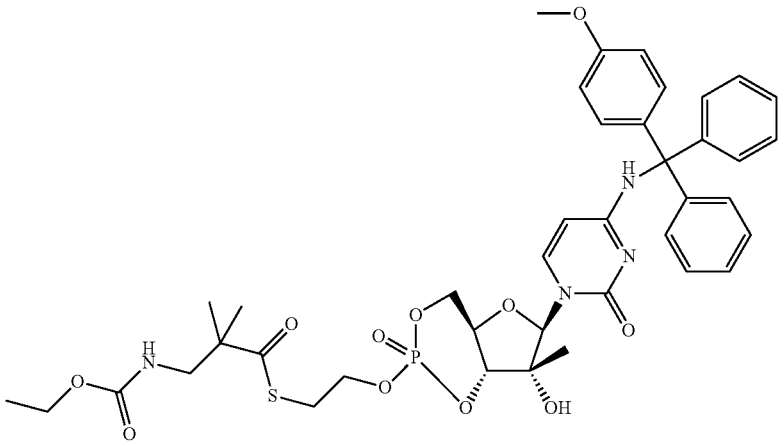
White solid; ^1H NMR (MeOD, 400 MHz) δ (ppm) 1.14 (s, 3H), 1.25 (d, J=6.24 Hz, 6H), 1.43 (t, J=7.04 Hz, 3H), 2.03 (quintuplet, J=6.64 Hz, 2H), 2.45 (t, J=7.25 Hz, 2H), 4.22-4.27 (m, 2H), 4.45-4.56 (m, 3H), 4.65-4.75 (m, 2H), 5 (septuplet, J=6.25 Hz, 1H), 5.95 (brs, 1H), 7.93 (s, 1H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −3.19 (s, 1P); MS (ESI) m/z=516.22 (MH^+).

(1): Diastereoisomer 2:

White solid; ^1H NMR (MeOD, 400 MHz) δ (ppm) 1.08 (s, 3H), 1.21 (d, J=6.27 Hz, 6H), 1.44 (t, J=7.05 Hz, 3H), 2.09

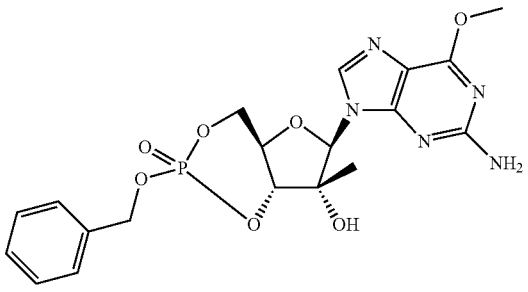
(quintuplet, J=6.50 Hz, 2H), 2.49 (t, J=7.01 Hz, 2H), 4.22-4.26 (m, 2H), 4.37-4.43 (m, 1H), 4.54 (t, J=7.04 Hz, 2H), 4.63-4.75 (m, 2H), 4.97 (septuplet, J=6.23 Hz, 1H), 6 (s, 1H), 8 (s, 1H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −4.97 (s, 1P); MS (ESI) m/z=516.22 (MH^+).

E-8e



Compound 5 (2 mmol) was dissolved in anhydrous pyridine (6.5 mL/mmol) under nitrogen and tetrazole solution (0.45M in CH_3CN) (6.5 mL/mmol) was added at room temperature. The solution was cooled down to −40° C. and a solution of 7c (2.60 mmol) in CH_3CN (10 mL) was added dropwise over 10 minutes. The reaction mixture was allowed to reach 0° C. over 1 hour and stirred at room temperature 30 minutes. To the reaction mixture was added a solution of tBuOOH (5M in decane)(0.5 mL/mmol) and the mixture was stirred at room temperature during 45 minutes. All solvents were removed under reduced pressure. The crude was diluted with AcOEt (200 mL) and washed with HCl 1N (2×200 mL), H_2O (200 mL) and brine (200 mL). The organic layer was filtered through a phase separator and concentrated under reduced pressure. The crude was purified by chromatography on a silica gel column (eluent: CH_2Cl_2/CH_3CH_2OH 0 to 4%) to give a mixture of 2 diastereoisomers in 13% yield. ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −6.43 (s, 0.42P), −4.95 (s, 0.58P); MS (ESI) m/z=823 (MH^+)

E-8g



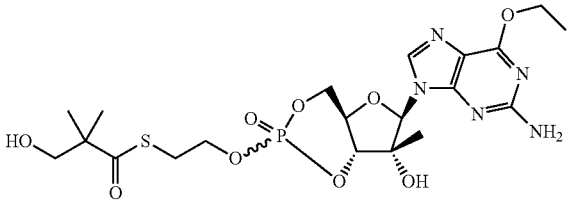
(2R,3R,4R,5R)-2-(2-amino-6-methoxy-purin-9-yl)-5-(hydroxymethyl)-3-methyl-tetrahydrofuran-3,4-diol (9.37 mmol) was dissolved in anhydrous pyridine (6.5 mL/mmol) under nitrogen and a solution of tetrazole 0.45M in acetonitrile (6.5 mL/mmol) was added at room temperature. The solution was cooled down to −10° C. and N-[benzyloxy-(diisopropylamino)phosphanyl]-N-isopropyl-propan-2-amine (9.37 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature during 3 hours and heated at 50° C. during 1 hour and at 35° C. overnight. tBuOOH (0.5 mL/mmol) was added at 35° C. and the mixture was stirred again during 5 hours. All solvents were removed under reduced pressure and the crude was purified several times by silica gel and C_{18} chromatographies to give the expected compound in 4% yield. MS (ESI) m/z=464.2 (MH^+).

General Procedure E:

The following procedure was used to obtain compounds 4, 5, 68, 69.

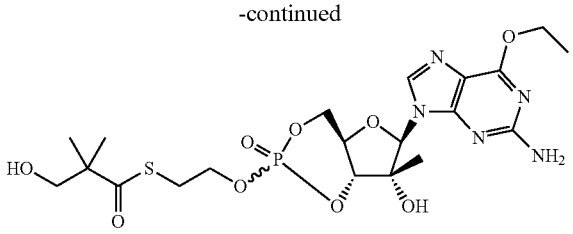
To a solution of compound E-8 (0.457 mmol) in CH_2Cl_2 (15 mL/mmol) was added TFA (1 mL/mmol) at room temperature during 10 minutes. The solvent was evaporated and the crude was directly loaded in chromatography on a silica gel column (eluent: CH_2Cl_2/CH_3OH 0 to 10%). The purified compound was submitted to preparative MS/HPLC to give the expected pure compounds.

4



Diastereoisomer 1

-continued



Diastereoisomer 2

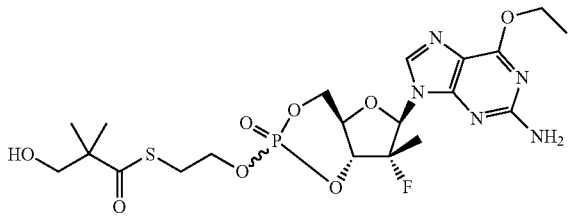
(4): Diastereoisomer 1:

White solid; ^{1}H NMR (MeOD, 400 MHz) δ (ppm) 1.11 (s, 3H), 1.20 (d, J=2.70 Hz, 6H), 1.45 (t, J=7.02 Hz, 3H), 3.59 (s, 2H), 4.23-4.28 (m, 2H), 4.38-4.45 (m, 1H), 4.55 (q, J=7.07 Hz, 2H), 4.64-4.77 (m, 2H), 6.02 (s, 1H), 8.01 (s, 1H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −5.35 (s, 1P); MS (ESI) m/z=548.04 (MH^+).

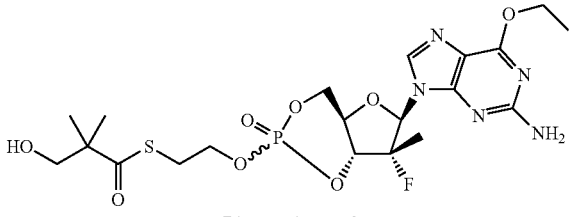
(4): Diastereoisomer 2:

White solid; ^{1}H NMR (MeOD, 400 MHz) δ (ppm) 1.04 (s, 3H), 1.14 (s, 6H), 1.34 (t, J=7.03 Hz, 3H), 3.14 (t, J=6.39 Hz, 2H), 3.51 (s, 2H), 4.12-4.17 (m, 2H), 4.41-4.47 (m, 3H), 4.56-4.68 (m, 2H), 5.39 (s, 1H), 5.86 (s, 1H), 7.83 (s, 1H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −3.57 (s, 1P); MS (ESI) m/z=548.04 (MH^+).

5



Diastereoisomer 1



Diastereoisomer 2

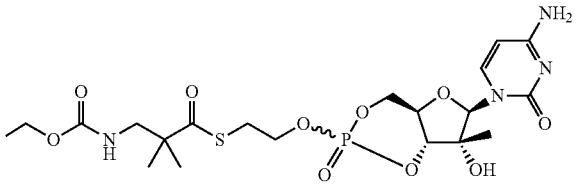
(5): Diastereoisomer 1:

White solid; ^{1}H NMR (MeOD, 400 MHz) δ (ppm) 1.20 (s, 3H), 1.21 (s, 3H), 1.36 (d, J=22.36 Hz, 3H), 1.45 (t, J=7.02 Hz, 3H), 3.59 (s, 2H), 4.26-4.31 (m, 2H), 4.35-4.42 (m, 1H), 4.55 (q, J=7.06 Hz, 2H), 4.68-4.76 (m, 2H), 5.38 (brs, 1H), 6.31 (d, J=19.88 Hz, 1H), 8.03 (s, 1H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −5.94 (s, 1P); ^{19}F NMR (MeOD, δ76.5 MHz) δ (ppm) −161.40 (1F); MS (ESI) m/z=550.2 (MH^+).

(5): Diastereoisomer 2:

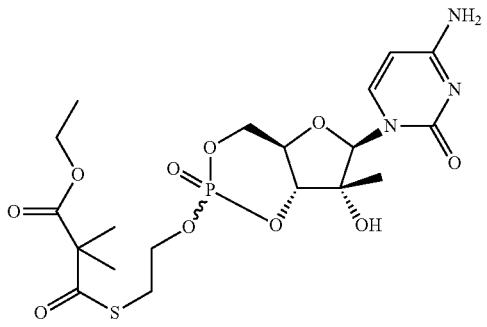
White solid; ^{1}H NMR (MeOD, 400 MHz) δ (ppm) 1.24 (s, 6H), 1.39 (d, J=23.28 Hz, 3H), 1.44 (t, J=7.03 Hz, 3H), 3.24 (t, J=6.37 Hz, 2H), 3.61 (s, 2H), 4.22-4.27 (m, 2H), 4.49-4.56 (m, 3H), 4.63-4.70 (m, 1H), 4.75-4.82 (m, 1H), 5.75 (brs, 1H), 6.26 (d, J=20.68 Hz, 1H), 7.95 (s, 1H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −3.92 (s, 1P); ^{19}F NMR (MeOD, δ76.5 MHz) δ (ppm) −160.57 (1F); MS (ESI) m/z=550.2 (MH^+).

67



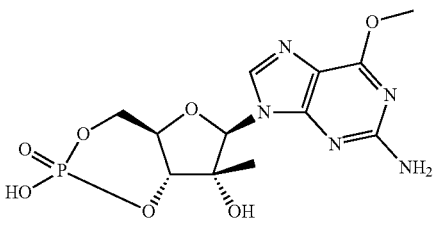
For this compound, the pure diastereoisomer was obtained after silica gel and C_{18} chromatography as a white solid in 28%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 1.03 (s, 3H), 1.13 (s, 6H), 1.14 (t, J=7.10 Hz, 3H), 3.11-3.16 (m, 4H), 3.96 (q, J=7.12 Hz, 2H), 4.06-4.12 (m, 2H), 4.27-4.34 (m, 2H), 4.58-4.68 (m, 2H), 5.73 (d, J=7.54 Hz, 1H), 5.87 (s, 1H), 6.08 (s, 1H), 7.16 (t, J=6.24 Hz, 1H), 7.22 (brs, 1H), 7.26 (brs, 1H), 7.62 (d, J=7.53 Hz, 1H); ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −4.91 (s, 1P); MS (ESI) m/z=551.15 (MH^+).

66



White solid; 67% yield; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 1.03 (s, 3H), 1.17 (t, J=7.09 Hz, 3H), 1.41 (s, 6H), 3.21 (t, J=6.36 Hz, 2H), 4.07-4.14 (m, 4H), 4.27-4.35 (m, 2H), 4.58-4.68 (m, 2H), 5.73 (d, J=7.55 Hz, 1H), 5.87 (s, 1H), 6.08 (s, 1H), 7.22 (brs, 1H), 7.26 (brs, 1H), 7.62 (d, J=7.53 Hz, 1H); ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −5.02 (s, 1P); MS (ESI) m/z=522.2 (MH^+).

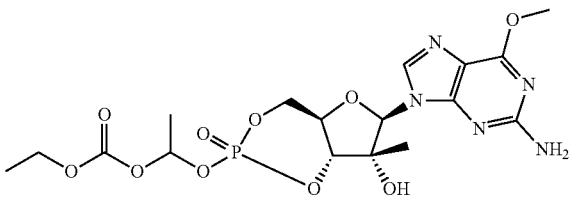
E-10



The compound E-8g (0.408 mmol) was stirred in anhydrous CH_3OH (10 mL) under nitrogen. The system was

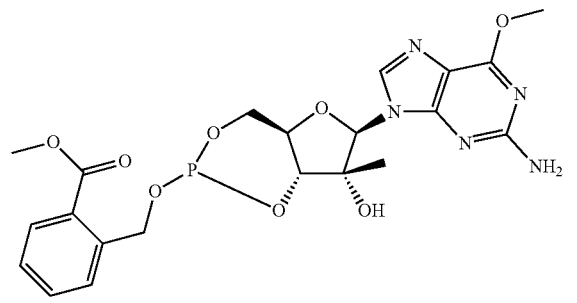
purged with nitrogen and vacuum and Pd/C 10% (20 mg) was added. The system was purged with nitrogen, vacuum and H_2 and the reaction mixture was stirred under H_2 atmosphere during 3 hours. The reaction mixture was diluted in CH_3OH and filtered through filter syringe 0.45 μm. The filtrate was concentrated under reduced pressure to give the expected compound as a white solid in quantitative yield. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm) 0.91 (s, 3H), 3.95 (s, 3H), 4.13-4.20 (m, 1H), 4.42-4.54 (m, 3H), 5.90-5.96 (m, 2H), 6.51 (brs, 2H), 8.08 (s, 1H); ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −5.71 (s, 1P); MS (ESI) m/z=374 (MH^+).

34



The compound E-10 (0.134 mmol) was stirred in anhydrous DMF (0.5 mL) under nitrogen. TEA (0.804 mmol) was added at room temperature and the reaction mixture was stirred 10 minutes before addition of 1-chloroethylethylcarbonate (0.67 mmol) and NaI (0.147 mmol). The reaction mixture was sealed and stirred at 60° C. during 5 hours. The reaction was cooled down to room temperature and AcOEt (60 mL) was added. The mixture was washed with brine (2×50 mL) and the organic phase was filtered through a phase separator. The solvent was removed under reduced pressure and the crude was purified by chromatography on a silica gel column (eluent: CH_2Cl_2/CH_3CH_2OH 0 to 5%) to give the expected compound as a mixture of diastereoisomers as a white solid in 15% yield. ^{31}P NMR (DMSO-d_6, 162 MHz) δ (ppm) −10.66−(−10.30) (m, 0.56P), −8.77 (s, 0.21P), −8.13 (s, 0.23P); MS (ESI) m/z=490.18 (MH^+).

E-12



(2R,3R,4R,5R)-2-(2-amino-6-methoxy-purin-9-yl)-5-(hydroxymethyl)-3-methyl tetrahydrofuran-3,4-diol (0.593 mmol) was solubilized in pyridine (3.95 mL) under nitrogen. A solution of tetrazole 0.45M in CH_3CN (1.78 mmol) was added at room temperature and the reaction mixture was cooled down to 0° C. before the addition of compound E-7e (0.771 mmol) in CH_3CN (0.5 mL). The mixture was stirred during 1 hour and H_2O (18.38 mmol) was added. The reaction mixture was stirred again during 40 minutes before concentration. The crude was purified by chromatography on a silica gel column (eluent: CH_2Cl_2/CH_3CH_2OH 0 to 10%) to give the expected compound in 17%. MS (ESI) m/z=506 (MH^+).

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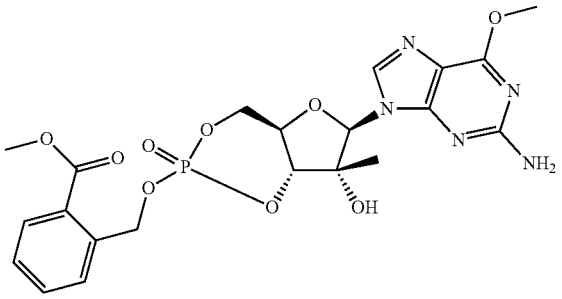
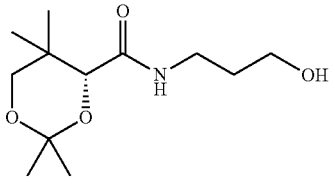


Compound E-12 (0.102 mmol) was dissolved in CH_3CN (1 mL) under nitrogen and tBuOOH (0.51 mmol) was added. The reaction mixture was stirred at room temperature during 1 hour. The reaction mixture was concentrated and the crude purified by chromatography on a silica gel column (CH_2Cl_2—CH_2Cl_2/CH_3CH_2OH (9/1) 0 to 4%) to give the expected compound as a white solid in 28%. ^1H NMR (MeOD, 400 MHz) δ (ppm) 0.95 (s, 3H), 1.28 (s, 3H), 3.34 (s, 1H), 3.91 (s, 3H), 4.05 (s, 3H), 4.36-4.42 (m, 1H), 4.64-4.72 (m, 2H), 5.49-5.54 (m, 1H), 5.58-5.63 (m, 1H), 5.98 (s, 1H), 7.46-7.50 (m, 1H), 7.60-7.64 (m, 1H), 7.69-7.71 (m, 1H), 7.93 (s, 1H), 7.99-8.01 (m, 1H); ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −5.09 (s, 1P); MS (ESI) m/z=522.12 (MH^+).

(4R)—N-(3-hydroxypropyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide (E-14)



D-panthenol (10 mmol), anhydrous Na_2SO_4 (35.20 mmol) and PTSA monohydrate (0.99 mmol) was stirred in anhydrous acetone (40 mL) at room temperature during 4 hours. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The crude was purified by chromatography on a silica gel column (eluent: CH_2Cl_2/CH_3OH 0 to 10%) to give the expected compound as a white crystallized solid in 59% yield. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm) 0.89 (s, 3H), 0.91 (s, 3H), 1.37 (s, 6H), 1.55 (quintuplet, J=6.52 Hz, 2H), 3.03-3.11 (m, 1H), 3.17-3.25 (m, 2H), 3.38-

3.43 (m, 2H), 3.63 (d, J=11.48 Hz, 1H), 4.02 (s, 1H), 4.49 (t, J=5.18 Hz, 1H), 7.45-7.48 (m, 1H).

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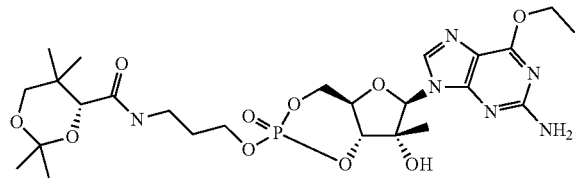

At 0° C. under nitrogen, to a solution of N—[chloro-(di-isopropylamino)phosphanyl]-N-isopropyl-propan-2-amine (0.986 mmol) and TEA (1.005 mmol) in anhydrous Et_2O (4 mL) was added compound E-14 (0.986 mmol). The reaction mixture was stirred at room temperature during 4 hours and then, filtered under nitrogen stream before concentration under reduced pressure to give a colorless crude oil. This oil was added to a solution of (2R,3R,4R,5R)-2-(2-amino-6-ethoxy-purin-9-yl)-5-(hydroxymethyl)-3-methyl-tetrahydrofuran-3,4-diol (0.615 mmol) and tetrazole 0.45M in CH_3CN (4 mL) in anhydrous pyridine (4 mL) at 0° C. Allowed to warm up to room temperature over 1 hour, the reaction mixture was heated at 50° C. during 1 hour. The reaction mixture was then cooled down to room temperature and tBuOOH 5-6M in decane (0.3 mL) was added. The reaction mixture was stirred at room temperature during 2 days. The solvents were evaporated and the crude was purified by chromatography on a silica gel column (eluent: CH_2Cl_2/CH_3OH 0 to 10%). A second purification by preparative MS/HPLC gave the expected compound as a white solid. ^{31}P NMR (MeOD, 162 MHz) δ (ppm) −4.84 (s, 0.65P), −3.14 (s, 0.35P); MS (ESI) m/z=615.2 (MH^+).

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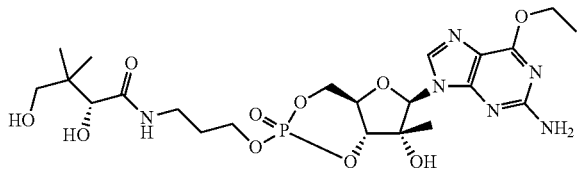
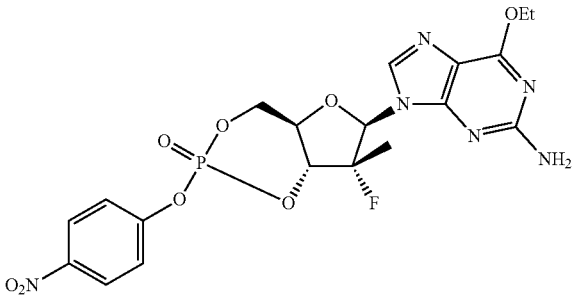


To a solution of compound 38 (0.0813 mmol) in a mixture CH_3OH/H_2O (0.20 mL/0.13 mL) was added PTSA (0.0042 mmol). The reaction mixture was stirred at room temperature during 24 hours and purified directly by preparative MS/HPLC to give the expected compound as white solid in 58% yield (mixture of diastereoisomers). ^1H NMR (CD_3CN, 400 MHz) δ (ppm) 0.84 (s, 1.9H), 0.86 (s, 1.1), 0.91 (s, 1.9H), 0.92 (s, 1.1H), 1.05 (s, 1.9H), 1.07 (s, 1.1H), 1.4 (t, J=7.09 Hz, 3H), 3.27-3.48 (m, 4H), 3.88 (s, 1H), 3.98-4.34 (m, 4H), 4.46-4.70 (m, 5H), 5.39 (brs, 2H), 5.9-5.93 (m, 1H), 7.19-7.27 (m, 1H), 7.70-7.85 (m, 1H); ^{31}P NMR (CD_3CN, 162 MHz) δ (ppm) −5.70 (s, 0.63P), −4.41 (s, 0.37P); MS (ESI) m/z=575.2 (MH^+).

E-17



To a solution of (2R,3R,4R,5R)-2-(2-amino-6-ethoxy-purin-9-yl)-5-(hydroxymethyl)-3-methyl-tetrahydrofuran-3,4-diol (3.06 mmol) and TEA (12.24 mmol) in THF (25 mL) at −78° C. under nitrogen was added 1-dichlorophosphoryloxy-4-nitro-benzene (3.97 mmol) and the mixture was allowed to warm up to 8° C. for 2 hours. The reaction was cooled down to −30° C. and NMI (15.3 mmol) was added dropwise. The resulting mixture was stirred at room temperature for an additional 1.5 hours. The solution was concentrated under reduced pressure and the residue purified by chromatography on a silica gel column (eluent: CH_2Cl_2/CH_3OH 0 to 2%) and by C_{18} chromatography to give the expected compound as a slightly yellow solid in 41% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.38 (d, J=22.18 Hz, 3H), 1.47 (t, J=7.10 Hz, 3H), 4.48-4.58 (m, 3H), 4.69-4.84 (m, 4H), 5.85 (brs, 1H), 6.04 (d, J=19.38 Hz, 1H), 7.52 (d, J=9.08 Hz, 2H), 7.62 (s, 1H), 8.31 (d, J=9.08 Hz, 2H); ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm) −13.24 (s, 1P); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ (ppm) −159.89 (1F); MS (ESI) m/z=511.2 (MH^+).

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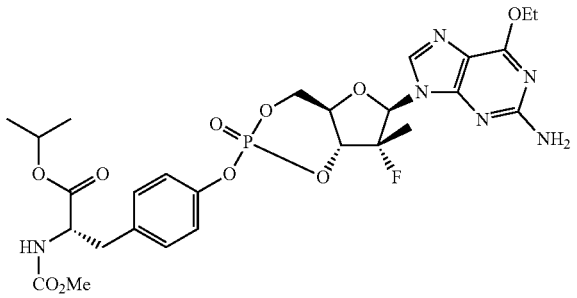


To a solution of tyrosine (0.294 mmol) in DMF (1 mL) were added NaH 60% in mineral oil (0.294 mmol) followed by compound E-17 (0.294 mmol). The reaction mixture was stirred at room temperature during 1 hour. A saturated NH_4Cl solution was added and the product was extracted with AcOEt (×2). The combined organic layers were dried, filtered and concentrated under reduced pressure. The crude was purified chromatography on a silica gel column (eluent: CH_2Cl_2/CH_3OH 0 to 3%) to give the expected pure compound as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.20 (d,

J=6.57 Hz, 3H), 1.22 (d, J=6.57 Hz, 3H), 1.40 (d, J=22.50 Hz, 3H), 1.46 (t, J=7.09 Hz, 3H), 3.03-3.14 (m, 2H), 3.67 (s, 3H), 4.37-4.43 (m, 1H), 4.52-4.60 (m, 3H), 4.62-4.72 (m, 2H), 4.96-5.08 (m, 3H), 5.18-5.20 (m, 1H), 5.86 (brs, 1H), 5.97 (d, J=19.66 Hz, 1H), 7.14-7.19 (m, 4H), 7.57 (s, 1H); ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm) −9.80 (s, 1P); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ (ppm) −159.03 (1F); MS (ESI) m/z=653.24 (MH^+).

Example 2

HCV Replicon Assay

Huh-7-derived cell line (Zluc) that harbors an HCV genotype 1b replicon and a luciferase reporter gene was grown in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum, 2 mM GlutaMAX, 1% MEM nonessential amino acids, 100 IU/mL penicillin, 100 μg/mL streptomycin, and 0.5 mg/mL Geneticin® (G418). For dose response testing the cells were seeded in 96-well plates at 7.5×10^3 cells per well in a volume of 50 μL, and incubated at 37° C./5% CO_2. Drug solutions were made up freshly in Huh-7 media as 2× stocks. Ten additional 5-fold dilutions were prepared from these stocks in DMEM without G418. At least three hours after Zluc cells were seeded, drug treatment was initiated by adding 50 μL of drug dilutions to the plates in duplicate. Final concentrations of drug ranged from 100 μM to 0.0000512 μM. Cells were then incubated at 37° C./5% CO_2. Alternatively, compounds were tested at two concentrations (1 μM and 10 μM). In all cases, Huh-7 (which do not harbors the HCV replicon) served as negative control. After 72 hours of incubation, the inhibition of HCV replication was measured by quantification of photons emitted after monooxygenation of 5'-fluoroluciferin to oxyfluoroluciferin by firefly luciferase. For this, media was removed from the plates via gentle tapping. Fifty microliters of ONE-glo luciferase assay reagent was added to each well. The plates were shaken gently for 3 min at room temperature and luminescence was measured on a Victor^3 V 1420 multilabel counter (Perkin Elmer) with a 1 second read time using a 700 nm cut-off filter. The EC_{50} values were calculated from dose response curves from the resulting best-fit equations determined by Microsoft Excel and XLfit 4.1 software. When screening at two fixed concentrations, the results were expressed as % inhibition at 1 μM and 10 μM.

For cytotoxicity evaluation, Zluc cells were treated with compound as described herein, and cell viability was monitored using the CellTiter-Blue Cell Viability Assay (Promega) by adding 20 μL of the assay solution to each well. The plates were then incubated at 37° C./5% CO_2 for at least 3 hours. Fluorescence was detected in plates using excitation and emission wavelengths of 560 and 590 nm, respectively, in a Victor^3 V 1420 multilabel counter (Perkin Elmer) and CC_{50} values were determined using Microsoft Excel and XLfit 4.1 software.

Compounds presented in Table 1 below were assayed according to the replicon assay described herein.

TABLE 1

Compound	HCV Replicon Activity		Compound	HCV Replicon Activity	
Reference	EC_{50}	CC_{50}	Reference	EC_{50}	CC_{50}
Compound 1 Diastereomer 1	+++	+	Compound 1 Diastereomer 2	++++	++
Compound 2 Diastereomer 1	++++	++	Compound 2 Diastereomer 2	+++	+

TABLE 1-continued

Compound	HCV Replicon Activity		Compound	HCV Replicon Activity	
Reference	EC_{50}	CC_{50}	Reference	EC_{50}	CC_{50}
Compound 3 Diastereomer 1	++++	++			
Compound 4 Diastereomer 1	++++	++	Compound 4 Diastereomer 2	++++	++
Compound 5 Diastereomer 1	++++	+	Compound 5 Diastereomer 2	++++	+
Compound 6 Diastereomer 1	++	+	Compound 6 Diastereomer 2	++++	+
Compound 7 Diastereomer 1	++++	+	Compound 7 Diastereomer 2	++++	++
Compound 8 Diastereomer 1	++++	+	Compound 8 Diastereomer 2	++++	+
Compound 9 Diastereomer 2	++++	+	Compound 10 Diastereomer 1	+++	+
Compound 11	++++	+	Compound 12 Diastereomer 1	++++	+
Compound 13	++++	+	Compound 13 Diastereomer 1	++++	+
Compound 13 Diastereomer 2	++++	+			
Compound 14 Diastereomer 1	++++	++	Compound 15	++++	+
Compound 16 Diastereomer 1	++++	++	Compound 16 Diastereomer 2	++++	++
Compound 17 Diastereomer 1	+++	+	Compound 17 Diastereomer 2	++++	++
Compound 18 Diastereomer 1	+++	+	Compound 18 Diastereomer 2	++++	++
Compound 19 Diastereomer 1	++++	++	Compound 19 Diastereomer 2	++++	++
Compound 20 Diastereomer 1	++++	+			
Compound 21	++++	+	Compound 21 Diastereomer 1	++++	+
Compound 22 Diastereomer 1	++++	+	Compound 22 Diastereomer 2	++++	+
Compound 23 Diastereomer 1	++++	++	Compound 23 Diastereomer 1	++++	++
Compound 24 Diastereomer 1	++++	++	Compound 24 Diastereomer 2	++++	++
Compound 25	+++	+	Compound 26	++++	+
Compound 27	++++	++	Compound 28	++++	++
Compound 29	++++	++	Compound 30	++	+
Compound 31	+++	+	Compound 32	++++	++
Compound 33	++++	++	Compound 34	++++	++
Compound 37	++++	++	Compound 38	++++	+
Compound 39	++++	++			

EC_{50} is provided as follows:
++++ ≤ 250 nM, 250 nM < +++ ≤ 1 μM, 1 μM < ++ ≤ 10 μM, and + > 10 μM
CC_{50} is provided as follows:
++ ≤ 50 μM, + > 50 μM

Example 3

Stability Assays

Abbreviations:

HLM=Human liver microsome; HIM=Human intestinal microsome; HLS9=Human liver S9 fraction; HIS9=Human intestinal S9 fraction; WB_H=Human whole blood; WB_M=Mouse whole blood; SGF=Simulated gastric fluid; SIF=Simulated intestinal fluid.

Stability in Simulated Gastric and Intestinal Fluids:

Simulated gastric and intestinal fluids containing pepsin and pancreatin respectively were prepared according to the U.S. Pharmacopoeia USP291 procedure (www.pharmacopeia.cn/v29240/usp29nf24s0_ris1s126.html). Compounds (final concentration 100 μM) were incubated in duplicate in the appropriate fluid for 2 hours at 37° C. The samples

were quenched with 200 µl cold acetonitrile, vortexed for 30 seconds and then centrifuged at 16,100 g for 10 min. The supernatants were analyzed by HPLC on a C-18 column with UV detection at 252 nm. The time 0 samples were prepared by adding SGF or SIF fluid to the quenching solvent followed by the test compound. Stability of the compounds was determined by peak area of the test compounds after incubation and calculated as percent of the peak area observed at time zero. Results are provided in Table 2 below.

Stability in Fresh Whole Blood:

Stability of compounds were determined in fresh human whole blood with K_2EDTA as the anticoagulant (stored refrigerated at 2-8° C. and used within 7 days of receipt). The experiment was conducted with three replicates for each time point. Whole blood, pre-incubated at 37° C. for 10-15 minutes, was fortified with a solution of test compound for a final concentration of 0.5 µM and mixed for 30 sec. At intervals (0, 0.5, 1 and 2 hr), three 50 µL aliquots were combined with 200 µL (each) of an ice-cold solution of the internal standard (carbutamide 500 ng/mL in acetonitrile). The samples were vortexed for 30 sec and then centrifuged at 16,100 g for 5 min. The supernatant was analyzed by LC-MS/MS. The MS peak area ratio of the test compounds versus the internal standard was calculated and percent unchanged test compound was calculated for each time point using this ratio. Results are provided in Table 2 below.

The stability in mouse blood was determined on ice at 0, 0.5 and 1 hr as herein. Results are provided in Table 2 below.

Stability in Liver Subcellular Fractions:

Stability of compounds were determined in subcellular fractions (microsomes) of human liver in duplicate for each matrix. Pooled liver microsomal proteins (1.0 mg/mL), suspended in incubation buffer (100 mM potassium phosphate, pH 7.4, 5 mM $MgCl_2$, and 0.1 mM EDTA), were preincubated for 5 min at 37° C. with 10 µM of a test compound from a 10 mM stock solution in DMSO (final DMSO concentration was 0.1%); the reaction was initiated by the addition of NADPH (3 mM final concentration). At specific times (0 and 60 min), 0.1 mL samples were taken and the reaction terminated by the addition of 4 volumes of stop solution (acetonitrile with 500 ng/mL carbutamide as an internal standard). The samples were vortexed for 30 sec and then centrifuged at 16,000 g for 10 min. 100 µL of supernatants were transferred to 96 deep-well plates preloaded with 100 µL distilled water and analyzed after mixing by LC-MS/MS. The MS peak area ratio of the test compounds versus the internal standard was calculated and percent unchanged test compound over 60 minutes was calculated using this ratio. Results are shown in Table 2.

TABLE 2

	Stability				
			Cells		
Compound	SGF	SIF	WB_Human (37° C.; 2 hr)	WB_Mouse (ice; 1 hr)	HLM (1 hr)
Compound 1 Diastereomer 1		105	73	79	
Compound 1 Diastereomer 2		83	87	1	
Compound 3 Diastereomer 1		92	20.5	14	
Compound 4 Diastereomer 1		105	82		
Compound 4 Diastereomer 2		77	59	105	
Compound 5 Diastereomer 1	108	86	82	99	
Compound 5 Diastereomer 2		77	46	93	
Compound 7 Diastereomer 1	87	50	25	1	0.5
Compound 8 Diastereomer 1		96	89		
Compound 8 Diastereomer 2		94	34		
Compound 9 Diastereomer 2	85	105	85		
Compound 10 Diastereomer 1			93		
Compound 13 Diastereomer 1		72	29	1	0.4
Compound 13 Diastereomer 2		72	70	1	
Compound 14 Diastereomer 1		88	62		
Compound 16 Diastereomer 2			54		
Compound 20 Diastereomer 1	98	95	98	1	0.35
Compound 21 Diastereomer 1		91	86		
Compound 22 Diastereomer 2		101	88		
Compound 24 Diastereomer 1	87	90	91		
Compound 24 Diastereomer 2	30	47	73		

Example 4

Metabolism Assays

Assay for the Release of Active Metabolite in Huh-7 Cells.

Huh-7 cells were plated in 1 mL culture medium (DMEM, containing glucose, L-glutamine and sodium pyruvate, 10% FBS, 100 IU/mL penicillin, 100 µg/mL streptomycin, 2 mM GlutaMAX, 1% MEM non-essential amino acids) at the concentration 0.8, 0.4 and 0.2 million cells per well on 6 well plates for 24, 48 and 72 hr treatment, respectively. Plated cells were incubated overnight at 37° C. in an incubator.

The following morning compounds was diluted to 20 µM from a stock solution in DMSO in fresh culture medium pre-warmed to 37° C. and 1 mL of the solution/well was added to cells. A final medium volume per well was 2.0 mL, Compound concentration in well was 10 µM and final DMSO concentration was 0.1%.

After 24, 48 or 72 hr, the medium was carefully removed and cell monolayers were washed twice with 2 mL ice-cold PBS per well. Following the last wash, all PBS was carefully removed and 1.0 mL of extraction solution (ice-cold 70% methanol) added. The plate was tightly covered with Parafilm, plastic plate cover and Parafilm again and an intracellular content was extracted at −20° C. for 24 hr.

After 24 hr extracts were transferred into polypropylene microfuge tubes and dried on a refrigerated centrivap concentrator. Dry residues were reconstituted in 250 µL of HPLC-grade water and centrifuged at 16,000×g for 10 min. Aliquots (100 µL each) of the supernatants were transferred into a 96 well plate and internal standard (4 ng/mL final concentration) was added as the internal standard (IS) for LC-MS/MS analysis.

Abbreviations:

FHH=fresh human hepatocytes; Ms=Mouse; MsH=Mouse hepatocyte.

Assay for the Release of Active Metabolite in Primary Hepatocytes:

Plates of fresh human and mouse hepatocytes were obtained on ice. The medium was removed and replaced with hepatocyte culture medium (William's E supplemented with penicillin-streptomycin, 1% L-glutamine, 1% insulin-transferrin-selenium and 0.1 μM Dexamethasone (Invitrogen) or with Invitro GRO HI medium complemented with Torpedo antibiotics (Celsis)). Cells were left overnight in an incubator at 37° C. to acclimatize to culture and the medium.

Hepatocyte incubations were conducted at a final volume of 0.5 mL hepatocyte culture medium/well (0.8 million cells/well for human and 0.5 million cells/well for mouse; 12 well plate no overlay, collagen coat). Culture medium from overnight incubation of cells was removed and replaced with fresh medium, pre-warmed to 37° C., containing 10 μM of test compound from a stock solution in DMSO (final DMSO concentration was 0.1%). At each specific time point, incubation medium was removed and cell monolayers were carefully washed two times with ice-cold PBS. Following the last wash, all PBS was carefully removed and 1.0 mL of extraction solution (ice-cold 70% methanol/30% water) added. Cells were scraped off and suspended in the extraction solution, transferred to 2 mL polypropylene microfuge tubes and intracellular contents extracted overnight at −20° C.

After the overnight treatment the cellular extracts were prepared by centrifugation at 16,000×g for 10 min to remove cellular debris. The remaining sample was then dried using a refrigerated centrivap concentrator. Dry extracts were reconstituted in 1000 μL of HPLC-grade water and centrifuged at 16,000×g for 10 min. Aliquots (100 μL each) of the supernatant were transferred into a 96 well plate and internal standard (4 ng/mL final concentration) was added as the internal standard (IS) for LC-MS/MS analysis.

The incubation time points were 6, 24 and 48 hours for human hepatocytes and 1, 4, 8, 12 and 24 hours for mouse hepatocytes. Results are provided in Table 3 below.

TABLE 3

Release of Active Metabolite in Hepatocytes

	Cells							
Compound	Huh-7 TP AUC (pmol/mill cells)	Huh-7 TP (24 hr)	Huh-7 TP (48 hr)	Huh-7 TP (72 hr)	FHH TP AUC (pmol · hr/mill cells)	FHH TP C_{max} (pmol/mill cells)	MsH AUC (pmol · hr/mill cells)	MsH C_{max} (pmol/mill cells)
Compound 1 Diastereomer 1					3425	85		
Compound 1 Diastereomer 2					10125	278	8363	330
Compound 2 Diastereomer 1							BLD[a]	BLD[a]
Compound 2 Diastereomer 2							656	33
Compound 3 Diastereomer 2					4574	146	3265	91
Compound 4 Diastereomer 1					4110	120	15078	468
Compound 4 Diastereomer 2					24086	681	13328	386
Compound 5 Diastereomer 1					7185	204	9866	374
Compound 5 Diastereomer 2					9694	448	8713	302
Compound 6 Diastereomer 1							BLD[a]	BLD[a]
Compound 6 Diastereomer 2							BLD[a]	BLD[a]
Compound 7 Diastereomer 1					377	31		
Compound 8 Diastereomer 1					BLD[a]	BLD[a]		
Compound 8 Diastereomer 2					BLD[a]	BLD[a]		
Compound 9 Diastereomer 2					BLD[a]	BLD[a]		
Compound 13 Diastereomer 1					1632	44		
Compound 13 Diastereomer 2					812	34		
Compound 14 Diastereomer 1					224	19		
Compound 15					1335	36		
Compound 20 Diastereomer 1					2393	88		
Compound 21 Diastereomer 1					BLD[a]	BLD[a]	BLD[a]	BLD[a]
Compound 22 Diastereomer 1					1247	44		
Compound 22 Diastereomer 2					742	28	BLD[a]	BLD[a]

TABLE 3-continued

Compound	Release of Active Metabolite in Hepatocytes: Cells: Huh-7 TP AUC (pmol/mill cells)	Huh-7 TP (24 hr)	Huh-7 TP (48 hr)	Huh-7 TP (72 hr)	FHH TP AUC (pmol · hr/ mill cells)	FHH TP C_{max} (pmol/mill cells)	MsH AUC (pmol · hr/ mill cells)	MsH C_{max} (pmol/mill cells)
Compound 24 Diastereomer 1					3399	154		
Compound 24 Diastereomer 2					3031	105		
Compound 25 Diastereomer 1	1697	25	28	36	2245	1137		
Compound 26 Diastereomer 1					BLD[a]	BLD[a]		

[a]BLD = below limit of detection

Example 5

Plasma and Liver Pharmacokinetics Following a Single Oral Dose in CD-1 Mice

Abbreviations:

Ms=Mouse; 2'-MeG=2'-methylguanosine; 2'-MeGTP=2'-methylguanosine triphosphate.

A single oral dose of test compound at 25 mg/kg in PEG 200 (dose volume 5 mL/kg) was administered to nine CD-1 male mice. Five untreated animals were used for the collection of control plasma and liver. Terminal plasma and liver samples were collected from three animals per time point at 4, 12 and 24 hours post dose. Liver specimens were collected from all animals immediately after the incision. Freezing forceps stored in liquid nitrogen were used to freeze the liver before excision.

Plasma samples were analyzed for 2'-methylguanosine (2'-MeG) by LC-MS/MS. The internal standard (IS) was 2'-MeG-D3. For protein precipitation and extraction, each plasma sample (50 μL) was treated with 500 μL of 0.2% formic acid in acetonitrile and 20 μL of the internal standard working solution. After vortexing and centrifugation, 500 μL of the sample extracts were transferred to a new plate, dried under N2 at ~28° C. and reconstituted with 75 μL of 0.2% FA in water. The extracts were chromatographed on an Aquasil C18 column using a gradient system of 0.2% formic acid in water and acetonitrile. The analytes were detected and quantified by tandem mass spectrometry in positive ion mode on an MDS Sciex API5000 equipped with a Turbo Ionspray® interface. The calibration range was 0.500 (LLOQ) to 200 ng/mL in mouse plasma. The corresponding range for molar units is 1.68 to 673 pmol/mL.

Liver samples were analyzed for the active species 2'-methylguanosine triphosphate (2'-MeGTP) by LC-MS/MS. 2'-MeGTP levels were assayed by homogenizing (on ice) a known weight of mouse liver with 4× volume of 0.95 M trichloroacetic acid (TCA). Internal standard solution was added to the homogenate followed by neutralization with 20% ammonium hydroxide solution and addition of 500 μL 1% formic acid. The tissue samples were extracted by weak anion exchange solid phase extraction (SPE). Post extraction, the eluates were evaporated under nitrogen, followed by reconstitution before injection onto the LC-MS/MS system. The samples were chromatographed on a Luna NH2 column using a gradient system of ammonium acetate (1 mM to 20 mM and pH 8.0 to pH 10.0) in water and acetonitrile (70:30). The analyte was detected and quantified by tandem mass spectrometry in positive ion mode on an API4000 equipped with a Turbo Ionspray® interface. The calibration range was 10 to 10000 pmol/mL in mouse liver homogenate (50 to 50000 pmol/g of mouse liver).

Results are provided in Table 4 below.

TABLE 4

Compound	Pharmacokinetics: Cells: Ms Plasma 2'-MeG Cmax (pmol/mL at 1 μmol/kg)	Ms Plasma 2'-MeG AUC (pmol · hr/mL at 1 μmol/kg)	Ms Liver 2'-MeGTP Cmax (pmol/g at 1 μmol/kg)	Ms Liver 2'-MeGTP AUC (pmol · hr/g at 1 μmol/kg)
Compound 1 Diastereomer 1	0.56	9	52	560
Compound 1 Diastereomer 2	8.6	68	640	7400
Compound 2 Diastereomer 1	1.5	21	180	1800
Compound 2 Diastereomer 2	0.64	9.9	63	790
Compound 3 Diastereomer 2	17	160	290	3200
Compound 4 Diastereomer 1	0.5	6.7	49	480
Compound 4 Diastereomer 2	1.7	24	78	1100
Compound 5 Diastereomer 1	8.1	97	130	1200
Compound 5 Diastereomer 2	23	220	250	2600
Compound 6 Diastereomer 1	1.3	13	3.7	35
Compound 6 Diastereomer 2	7.2	54	59	530
Compound 20 Diastereomer 1	5.9	58	49	410

Example 6

Hydrolysis of D-Alanine Prodrugs by Cathepsin a (CatA) and/or Carboxylesterase 1 (CES1)

Introduction

The HCV NS5B RNA-dependent RNA polymerase is essential for the viral life cycle and thus, is a target for antiviral therapy. The active site of NS5B is well conserved among the six genotypes of HCV and therefore, nucleos(t)ide analogs can act pan-genotypically. Furthermore, nucleotide inhibitors are typically not cross-resistant to other classes of direct acting antivirals and can have a higher barrier to resis-

tance compared to non-nucleoside, protease and non-structural protein 5A (NS5A) inhibitors of HCV, making this class of HCV antivirals useful in a of combination HCV antiviral therapy.

Nucleoside analogs are typically competitive inhibitors of endogenous nucleosides and may act through chain termination upon incorporation into the nascent HCV RNA chain during replication (Eldrup, et al. 2004, Structure-Activity Relationship of Purine Ribonucleosides for Inhibition of Hepatitis C Virus RNA-Dependent RNA Polymerase. J. Med. Chem. 47: 2283-2295). However, upon cell entry a nucleoside analog must first be phosphorylated to the active triphosphate species (Gardelli, et al 2009, Phosphoramidate prodrugs of 2'-C-methylcytidine for therapy of hepatitis C virus infection. J. Med. Chem. 52:5394-5407; Stein and Moore, 2001, Phosphorylation of nucleoside analog antiretrovirals: a review for clinicians. Pharmacotherapy 21:11-34; Tomassini, et al 2005, Inhibitory effect of 2'-substituted nucleosides on hepatitis C virus replication correlates with metabolic properties in replicon cells. Antimicrob. Agents Chemother. 49:2050-2058; Murakami, et al 2007, Mechanism of activation of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine and inhibition of hepatitis C virus NS5B RNA polymerase. Antimicrob. Agents Chemother. 51:503-509). A barrier to first generation nucleoside inhibitors was the often inefficient conversion of the nucleoside to a nucleotide monophosphate (NMP) by cellular kinases (Gardelli, et al 2009, Phosphoramidate prodrugs of 2'-C-methylcytidine for therapy of hepatitis C virus infection. J. Med. Chem. 52:5394-5407; Stein and Moore, 2001, Phosphorylation of nucleoside analog antiretrovirals: a review for clinicians. Pharmacotherapy 21:11-34; Murakami, et al 2007, Mechanism of activation of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine and inhibition of hepatitis C virus NS5B RNA polymerase. Antimicrob. Agents Chemother. 51:503-509).

Second generation nucleoside analogs have been designed as liver-targeted nucleotide prodrugs, which bypass the rate-limiting NMP conversion to active species by delivering the nucleoside as a monophosphate prodrug. As GS-7977, Z4 and Z2 are pyrimidine nucleotide prodrugs that act by inhibition of the HCV NS5B RNA-dependent RNA polymerase through a 2' modified UTP metabolite.

The intracellular metabolism (anabolism) of nucleotide analogs is critical to their antiviral activity. A first step in the metabolism of nucleotide prodrugs is the removal of the prodrug moiety by cellular enzymes followed by the activation of the nucleoside monophosphate analog by host cell kinases for the sequential phosphorylation of the parent nucleos(t)ide analog to the 5'-triphosphate form, the biologically active metabolite. Removal of the prodrug moiety often involves sequential or independent work of different cellular enzymes.

In vivo Z4 and Z2 appear to be effectively liver-targeted with a high liver:plasma ratio of drug metabolites. Both prodrugs are readily converted to the triphosphate (TP) metabolite in the liver of mice and monkey producing more TP than GS-7977. The TP derivatives of Z4 and Z2 selectively inhibit wild-type HCV NS5B enzyme in vitro with submicromolar IC_{50} values. When tested in a genotype 1b HCV replicon-bearing human hepatoma cell line (Huh-7), however, Z4 and Z2 were largely inactive and failed to inhibit replicon reproduction (EC_{50}>50 μM). The in vitro antiviral inactivity of Z4 and Z2 is thought to reflect an inability of Huh-7 replicon cells to metabolize the prodrug moiety.

The first step of GS-7977 activation includes hydrolysis of the carboxyl ester by cathepsin A (CatA) and/or carboxylesterase 1 (CES1) (Saboulard et al, 2009, Characterization of the Activation Pathway of Phosphoramidate Triester Prodrugs of Stavudine and Zidovudine. Molecular Pharmacology. 56:693-704; Murakami et al, 2010, Mechanism of Activation of PSI-7851 and Its Diastereoisomer PSI-7977, JBC, 285(45):34337-34347; Sofia et al, 2010, Discovery of PSI-35366, a novel purine nucleotide prodrug for the treatment of hepatitis C virus. J Med. Chem. 53:7202-7218). Since CES1 is reported to be underexpressed in Huh-7 replicon cells, CatA appears to be the major enzyme that hydrolyzes GS-7977 in these cells (Murakami et al, 2010, Mechanism of Activation of PSI-7851 and Its Diastereoisomer PSI-7977, JBC, 285(45):34337-34347).

Methods

In this example the hydrolysis of the two D-ala-McGuigan prodrugs Z2 (2'-C1,2'-MeUMP, diastereoisomer R_P) and Z4 (2'-F, 2'-MeUTP, diastereoisomer R_P) using CatA and CES1 was compared with activation of the L-ala-McGuigan prodrugs Y1 (2'-MeUTP, S_P stereoisomer), GS-7977 (X1, diastereoisomer S_P) and PSI-7976 (X2, diastereoisomer R_P).

CatA, cathepsin L (CatL) and CES1 were purchased from R & D Systems (Minneapolis, Minn.). Prior to the enzymatic hydrolysis reactions, CatA was activated according to the manufacturer's instruction. Briefly, CatA (0.05 μg/μL) was incubated with CatL (0.005 μg/μL) for 30 min at 37° C. in 25 mM MES pH 6.0 containing 5 mM DTT. The reaction was stopped by addition of the CatL specific inhibitor E64 (10 μM).

The CatA assay was performed at 37° C. The reaction mixture contained 25 mM MES buffer pH 6.0, 100 mM NaCl, 4 mM DTT and 100 μM of the compound. The reaction was started by addition of the activated CatA enzyme to a final concentration of 0.005 μg/μL. One hundred-μL aliquots were taken after 0.5 min, 3 hrs and 18 hrs of incubation. Reactions were stopped by mixing the sample with an equal volume of ice-cold methanol, and were loaded on a HPLC for analysis.

CES1 assay was performed at 37° C. in the reaction mixture containing 50 mM Tris/HCl buffer pH 7.5 and 100 μM of the compound. Reaction was started by addition of the CES1 to the final concentration 0.01 μg/mL. 100 μL aliquots were taken after 0.5 min, 3 hrs and 21 hrs of the incubation and the reaction was stopped by mixing with 100 μl of the ice-cold methanol prior to HPLC analysis.

Samples were analyzed by HPLC using 5μ C-18, 4.6×250 mm Phenomenex® Columbus column (Phenomenex USA, CA). The mobile phase consisted of buffer A (25 mM potassium phosphate with 5 mM tetrabutylammonium dihydrogen phosphate pH 6.3) and buffer B (100% methanol). HPLC gradient conditions are shown in Table 4.

TABLE 4

Time (min)	% A	% B	Flow (mL/min)
0	100	0	1
15	70	30	1
30	50	50	1
65	50	50	1
70	95	5	1

Results

As shown in Table 5, both CatA and CES1 hydrolyzed GS-7977 and its diastereoisomer PSI-7076. However, CatA cleaved GS-7977 (S_P configuration) 10 times more efficiently than its R_P diastereoisomer, while CES1 preferentially hydrolyzed the R_P diastereoisomer PSI-7976. These results are in good agreement with the literature (Murakami, et al 2010, Mechanism of Activation of PSI-7851 and Its Diastereoisomer PSI-7977, JBC, 285(45):34337-34347).

TABLE 5

Compound	Reference number	S_P/R_P	EC_{50}, (μM)	Huh-7 pmol * hr/ 10^6cellsAUC_{0-72}	Liver TP pmol * hr/g	CatA	CES1
GS-7977 L-Ala-2'F,2'MeUTP	X1	S_P	0.25	63555	250	100% @ 18 h	12%/3 h; 15%/21 h
PSI-7976 L-Ala-2'F,2'MeUTP	X2	R_P	2.08	6527	310	10% @ 18 h	56%/3 h; 94%/21 h
L-Ala-2'MeUTP	Y1	S_P	0.17	63740	420	100 @ 3 h	Not tested
D-Ala-2'Cl,2'MeUTP	Z1	S_P	7		4400	0%	4.5% @ 21 h
	Z2	R_P	5.9; 14; 47	436.9	6200	0%	23% @ 3 h; 49% @ 21 h
D-Ala-2'F,2'MeUTP	Z3	S_P	17		430	0%	0%
	Z4	R_P	>50	720.4	3200	0%	10% @ 3 h; 26% @ 21 h

In contrast, CatA was unable to hydrolyze any of the D-Ala-prodrugs tested. However, both Z2 and Z4 were processed by CES1.

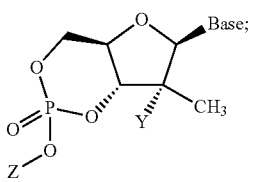
Since Huh-7 replicon-bearing cells have been found to express little or no CES1, CatA is the major enzyme that hydrolyzes GS-7977 in these cells (Murakami et al, 2010, Mechanism of Activation of PSI-7851 and Its Diastereoisomer PSI-7977, JBC, 285(45):34337-34347). The inability of CatA to activate the D-Ala-prodrugs Z2 and Z4 may explain the inactivity of these compounds in Huh-7 replicon-bearing cells, since the lack of in vitro activity is believed to reflect low production of the active TP moiety in Huh-7 replicon cells.

In vivo, high expression of CES1 in the liver coupled with high catalytic efficiency and possible involvement of other liver enzyme appears to result in efficient conversion of Z2 and Z4 to their corresponding triphosphate metabolites.

All publications, patents, and patent applications cited in this specification are herein incorporated by reference as if each individual publication, patent, or patent application were specifically and individually indicated to be incorporated by reference. While the claimed subject matter has been described in terms of various embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions, and changes may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the claimed subject matter is limited solely by the scope of the following claims, including equivalents thereof.

What is claimed is:

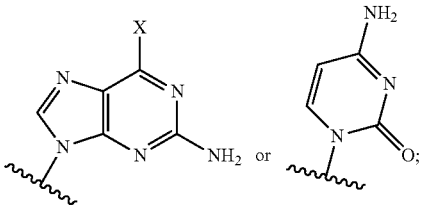
1. A compound of Formula (VIII):



(VIII)

or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, wherein:

each Base is independently



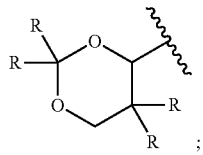
each X is independently alkoxyl, hydrogen, or hydroxyl;

each Y is independently hydroxyl, acetoxyl, or fluoro;

each Z is independently -LC(O)O(L)$_p$C(R)$_3$, -L-Ar—C(O)O(L)$_p$C(R)$_3$, —C(R)(E)(L)$_p$OC(O)O(L)$_p$C(R)$_3$, -LSC(O)LOH, -LSC(O)LOC(O)(L)$_p$C(R)$_3$, -LSC(O)LOC(O)(L)$_p$N(R)$_2$, -LS-S(L)$_p$C(R)$_3$, -LS-SLOH, -LN(R)C(O)O(L)$_p$C(R)$_3$, -LSC(O)LN(R)C(O)O(L)$_p$C(R)$_3$, —Ar—B, -L-B, -LN(R)C(O)D, -LN(R)C(O)CH(OH)(C(R)$_2$)$_2$OH, -(L)$_p$C(R)(R^A)C(O)O(L)$_p$C(R)$_3$, or -LSC(O)LC(O)O(L)$_p$C(R)$_3$;

each B is independently an alkyl group substituted with aminocarboxylene, carboxylene, or both;

each D is independently



;

each E is independently alkyl, aryl, or heteroaryl;

each Ar is independently an arylene or heteroarylene;

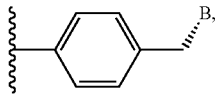
each L is independently alkylene;

each R is independently hydrogen, alkyl, aryl, or heteroaryl; each R^A is independently a carbocyclic or heterocyclic ring; and

each p is independently 0 or 1.

2. The compound of claim **1**, wherein each Z is independently —(C$_{1-10}$)alkylene-SC(O)(C$_{1-10}$)alkyleneC(O)O[(C$_{1-10}$)alkylene]$_p$C(R)$_3$, —(C$_{1-10}$)alkylene-SC(O)(C$_{1-10}$)alkyleneN(R)C(O)O[(C$_{1-10}$)alkylene]$_p$C(R)$_3$, —(C(R)$_2$)$_m$C(O)O(C(R)$_2$)$_n$C(R)$_3$, —(C(R)$_2$)$_m$ArC(O)O(C(R)$_2$)$_n$C(R)$_3$, —C(R)(E)(C(R)$_2$)$_n$OC(O)O(C(R)$_2$)$_n$C(R)$_3$, —(C(R)$_2$)$_m$SC(O)(C(R)$_2$)$_m$OH, —(C(R)$_2$)$_m$SC(O)(C(R)$_2$)$_m$OC(O)

$(C(R)_2)$—$C(R)_3$, —$(C(R)_2)_mS$—$S(C(R)_2)_nC(R)_3$, —$(C(R)_2)_mS$—$S(C(R)_2)_mOH$, —$(C(R)_2)_mN(R)C(O)O(C(R)_2)$—$C(R)_3$,



—$(C(R)_2)_nB$, —$(C(R)_2)_mN(R)C(O)D$, —$(C(R)_2)_mN(R)C(O)CH(OH)(C(R)_2)_2OH$, or —$(C(R)_2)_nC(R)(R^A)C(O)O(C(R)_2)_nC(R)_3$; wherein each m is 1-10, each n is 0-10, and each p is 0 or 1.

3. The compound of claim **1**, wherein:

each B is independently $C(R)_3(C(R)_2)_nOC(O)C(R)(B—)N(R)C(O)O(C(R)_2)_nC(R)_3$;

where B— denotes the attachment position to Ar or L; and

each n is independently an integer selected over the range of 0 to 10.

4. The compound of claim **1**, wherein each E is independently C_1-C_{10} alkyl, C_5-C_{10} aryl, or C_5-C_{10} heteroaryl.

5. The compound of claim **1**, wherein each Ar is independently C_5-C_{10} arylene or C_5-C_{10} heteroarylene.

6. The compound of claim **1**, wherein each R is independently hydrogen, C_1-C_{10} alkyl, C_5-C_{10} aryl, or C_5-C_{10} heteroaryl.

7. The compound of claim **1**, wherein each R^A is independently a 3-20 membered carbocyclic or heterocyclic ring.

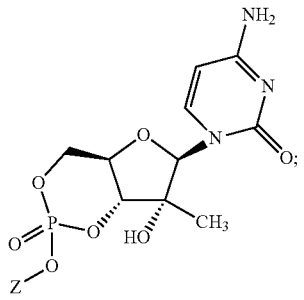
8. The compound of claim **1** wherein Y is fluoro.

9. The compound of claim **1** wherein Y is acetoxyl.

10. The compound of claim **1** wherein Y is hydroxyl.

11. The compound of claim **1** according to Formula (IX):

(IX)



or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof.

12. The compound of claim **11**, wherein each Z is independently -$LSC(O)LC(O)O(L)_pC(R)_3$ or -$LSC(O)LN(R)C(O)O(L)_pC(R)_3$.

13. A pharmaceutical composition comprising the compound of claim **1** and a pharmaceutically acceptable excipient, carrier or diluent.

14. The pharmaceutical composition of claim **13**, wherein the composition is an oral formulation.

15. A method for the treatment of a host infected with a hepatitis C virus, comprising the administration of an effective treatment amount of a compound or composition of claim **1**.

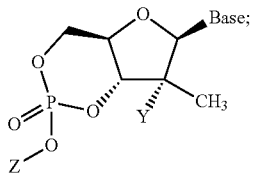
16. The method of claim **15**, wherein the host is a human.

17. The method of claim **15**, wherein the administration directs a substantial amount of the compound or pharmaceutically acceptable salt thereof, to a liver of the host.

18. The method of claim **15**, wherein the compound or composition is administered in combination or alternation with a second anti-viral agent selected from the group consisting of an interferon, a nucleotide analogue, a polymerase inhibitor, an NS3 protease inhibitor, an NS5A inhibitor, an entry inhibitor, a non-nucleoside polymerase inhibitor, a cyclosporine immune inhibitor, an NS4A antagonist, an NS4B-RNA binding inhibitor, a locked nucleic acid mRNA inhibitor, a cyclophilin inhibitor, and combinations thereof.

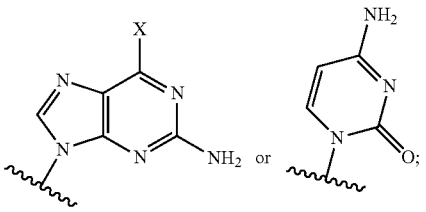
19. A compound of Formula (VIII):

(VIII)



or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, wherein:

each Base is independently



each X is alkoxyl of formula —OR', wherein R' is C_{1-10} alkyl or C_{3-15} cycloalkyl;

each Y is independently hydroxyl, acetoxyl, or fluoro;

each E is independently C_{1-10} unsubstituted alkyl, C_{1-10} substituted alkyl, aryl, or heteroaryl;

each Ar is independently C_5-C_{10} arylene or C_5-C_{10} heteroarylene;

each L is independently straight-chained or branched C_1-C_{10} unsubstituted alkylene or C_1-C_{10} substituted alkylene;

each R is independently C_{1-10} unsubstituted alkyl, C_{1-10} substituted alkyl, aryl, or heteroaryl;

each Z is independently -$LC(O)O(L)_pC(R)_3$, -L-Ar—$C(O)O(L)_pC(R)_3$, —$C(R)(E)(L)_pOC(O)O(L)_pC(R)_3$, -$LSC(O)LOH$, -$LSC(O)LOC(O)(L)_pC(R)_3$, -$LSC(O)LOC(O)(L)_pN(R)_2$, -LS-$S(L)_pC(R)_3$, -LS-SLOH, -$LN(R)C(O)O(L)_pC(R)_3$, -$LSC(O)LN(R)C(O)O(L)_pC(R)_3$, —Ar—B, -L-B, -$LN(R)C(O)D$, -$LN(R)C(O)CH(OH)(C(R)_2)_2OH$, or -$(L)_pC(R)(R^A)C(O)O(L)_pC(R)_3$; wherein each p is 0 or 1;

wherein

each C_{1-10} substituted alkyl is independently C_{1-10} alkyl substituted by a moiety which is halogen, fluoro, chloro, bromo, iodo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate;

each aryl is independently phenyl, biphenyl, and naphthyl, unsubstituted or substituted by a moiety which is halogen fluoro, chloro, bromo, iodo, alkyl, haloalkyl, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate

each heteroaryl is independently furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl, triazolyl, benzofuranyl, benzimidazolyl, benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzotriazolyl, benzoxazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indolizinyl, indolyl, indazolyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinolinyl, quinoxalinyl, quinazolinyl, thiadiazolopyrimidyl, thienopyridyl, acridinyl, benzindolyl, carbazolyl, dibenzofuranyl, perimidinyl, phenanthrolinyl, phenanthridinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, or xanthenyl.

20. The compound of claim **19**, wherein each straight-chained or branched C_{1-10} unsubstituted alkylene is independently methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, t-butylene, pentylene, isopentylene, neopentylene, hexylene, isohexylene, 3-methylpentylene, 2,2-dimethylbutylene, or 2,3-dimethylbutylene.

21. The compound of claim **19**, wherein

each X is alkoxyl of formula —OR', wherein R' is C_{1-10} alkyl or C_{3-15} cycloalkyl;

each E is independently C_{1-10} unsubstituted alkyl, C_{1-10} substituted alkyl, aryl, or heteroaryl;

each Ar is independently C_5-C_{10} arylene or C_5-C_{10} heteroarylene;

each L is independently C_1-C_{10} substituted alkylene;

each R is independently C_{1-10} unsubstituted alkyl, C_{1-10} substituted alkyl, aryl, or heteroaryl;

wherein

each C_{1-10} substituted alkyl is independently C_{1-10} alkyl substituted by a moiety which is halogen, fluoro, chloro, bromo, iodo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate;

each C_{1-10} substituted alkylene is independently C_{1-10} alkylene substituted by a moiety which is halogen, fluoro, chloro, bromo, iodo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate;

each aryl is independently phenyl, biphenyl, and naphthyl, unsubstituted or substituted by a moiety which is halogen fluoro, chloro, bromo, iodo, alkyl, haloalkyl, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate;

each heteroaryl is independently furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl, triazolyl, benzofuranyl, benzimidazolyl, benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzotriazolyl, benzoxazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indolizinyl, indolyl, indazolyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinolinyl, quinoxalinyl, quinazolinyl, thiadiazolopyrimidyl, thienopyridyl, acridinyl, benzindolyl, carbazolyl, dibenzofuranyl, perimidinyl, phenanthrolinyl, phenanthridinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, or xanthenyl.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

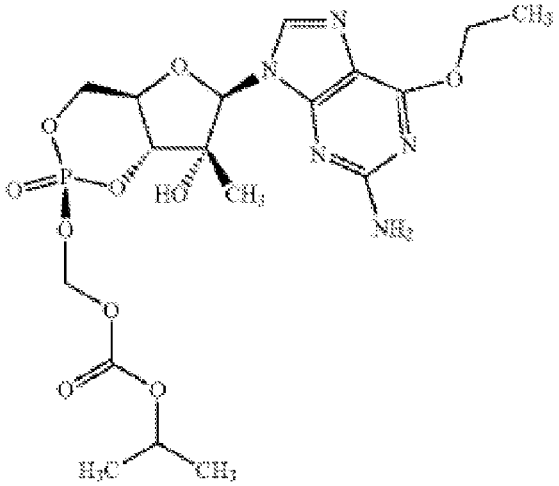
CERTIFICATE OF CORRECTION

PATENT NO. : 9,296,778 B2
APPLICATION NO. : 13/899487
DATED : March 29, 2016
INVENTOR(S) : Christophe Claude Parsy et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

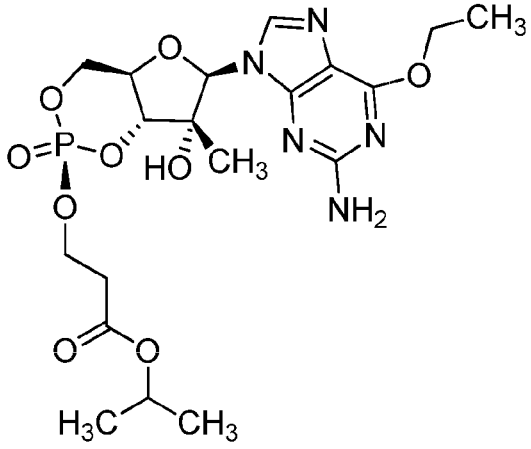
In The Specification

In column 80, at the bottom, please delete the following formula:



"

and insert the following formula:



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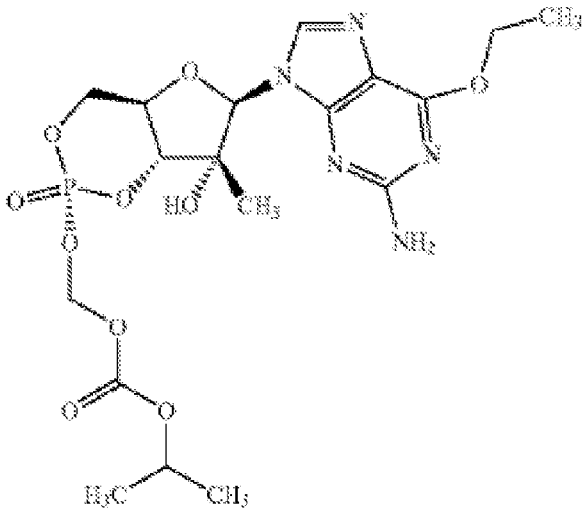
Signed and Sealed this
Fourth Day of October, 2016

Michelle K. Lee

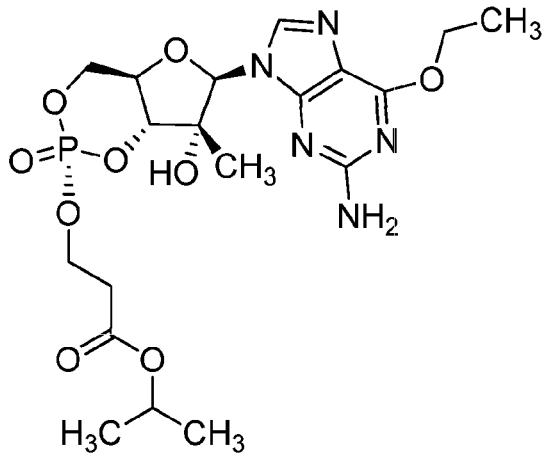
Michelle K. Lee
Director of the United States Patent and Trademark Office

In column 81, at the top, please delete the following formula:



“ ”

and insert the following formula:



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